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Why Lilly's Derica Rice

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MAY 2016

Why Lilly's Derica Rice Isn't Your Typical CFO

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DERICA RICE
CFO, Eli Lilly and Company

Tracks Of Growth

Lilly's chairman, president, and CEO, John Lechleiter, discusses how the company will meet its promised performance goals in 2018.

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Life Science Leader

MAY 2016 VOL. 8 NO. 5

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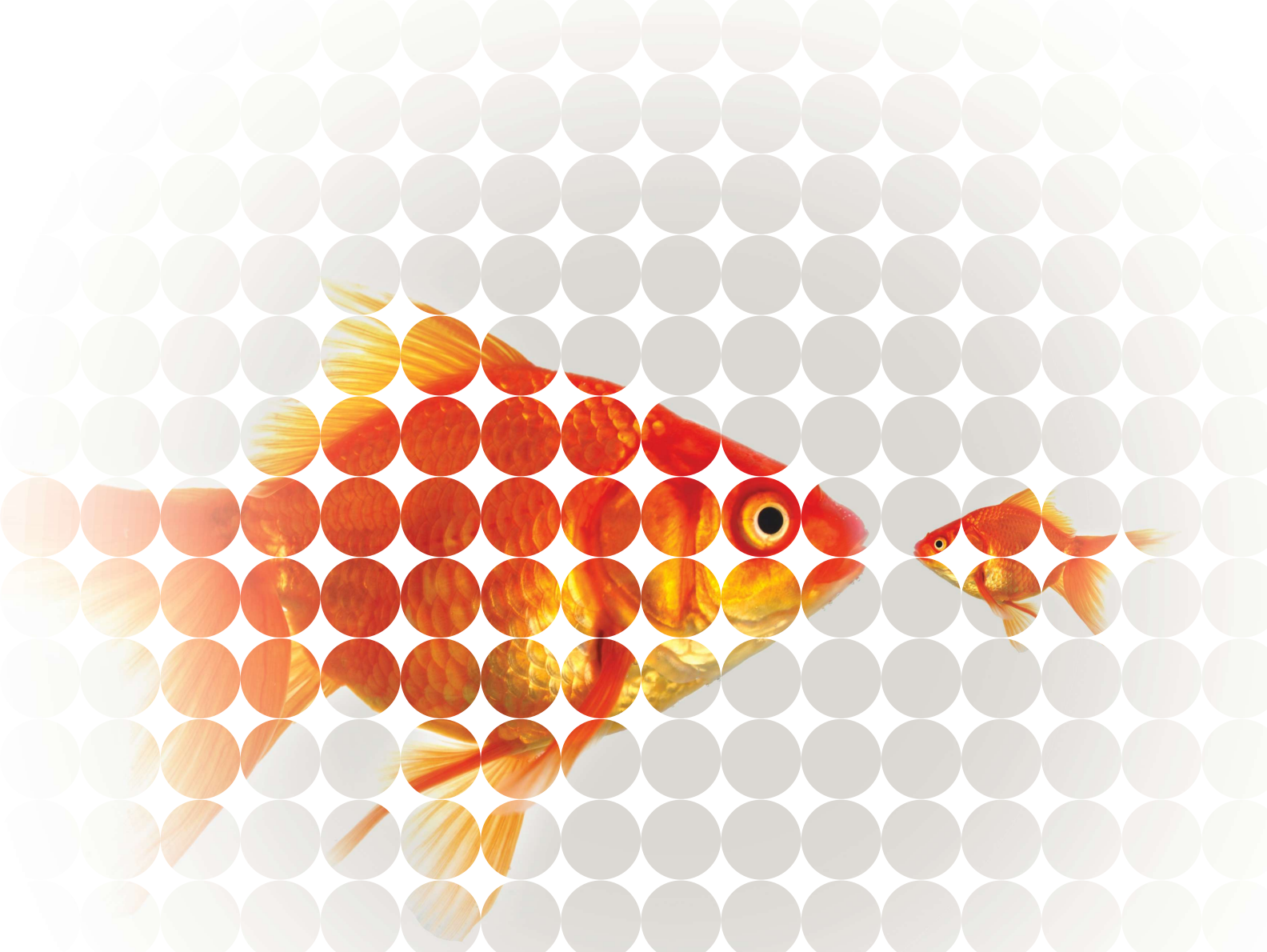
LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 8, No. 5 is published monthly by Jameson Publishing, Inc. at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5580. Periodical postage paid at Erie, PA 16510 and additional mailing offices. **SUBSCRIPTION RATES** For U.S. based subscribers, $295 for one year. If your mailing address is outside the U.S. the subscription price is $445 for one year. **POSTMASTER:** Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. **PUBLICATIONS AGREEMENT:** No. 40722524 c/o AIM, 7289 Torbram Road, Mississauga, ON L4T 1G8.



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Is Going Against The Grain
A Good Business Idea?

ROB WRIGHT Chief Editor

My grandfather made his living as a carpenter. When it came to smoothing wood (especially expensive hardwoods) he knew that the best results were achieved by running his tool with the grain, not against it. This carpenters' wisdom has since become a popular idiom (i.e., going against the grain) and is often used in reference to people or companies opting to do the opposite of what is expected. We all know that in life, as in business, there are times when it is much easier to simply "go along to get along." But have you ever wondered when going against the grain of conventional wisdom is a good *business* idea? Consider the following example.

Warby Parker is an American brand of prescription eyeglasses and sunglasses. When founded in 2010, the company was starting in an industry where Luxottica controlled more than 80 percent of the global eyeglass market. Upon mentioning their business idea (i.e., taking on a monopoly by designing, producing, and selling glasses at wholesale prices directly to customers) to friends and family, these "wantrepreneurs" found themselves being blasted. Sure Zappos had pulled off a similar business model with shoes, but if doing the same with eyeglasses was such a good idea, wouldn't it have been done already? Six years later, this private, venture-backed company is valued at over $1.2 billion, and sits atop *Fast Company*'s most innovative list for 2015, ahead of both Apple and Google. While there are numerous other examples of businesses in other industries going against the grain and being highly successful, what about one a little closer to home (i.e., the traditionally conservative biopharmaceutical industry)?

When John Lechleiter took over as Lilly CEO in 2008, he and other members of the company's executive committee could see a patent cliff storm brewing on the horizon. Though the company had survived the loss of Prozac, a product that generated approximately 30 percent of Lilly's total revenues, the patent loss time period spanning 2011 – 2014 looked much bleaker. The four products (i.e., Zyprexa, Humalog, Cymbalta, and Evista) set to expire during what Lilly insiders began referring to as "years YZ" represented about 40 percent of revenue! Conventional wisdom seemed to suggest M&A as the solution to Lilly's patent cliff/empty pipeline problem. After all, company peers facing similar scenarios (e.g., Merck, Pfizer) were taking this approach, and they were not alone. In fact, from 2012 through the end of 2013, the biopharmaceutical sector executed 253 M&A deals. While analysts and investors advocated Lilly consider doing the same, the company went against the grain and instead opted to focus its efforts on R&D — a bold move that seems to be paying off.

Lilly's willingness to go against the grain inspired *Life Science Leader* to do the same. Usually when you flip through the pages of our publication, you will find features involving a variety of different companies. This month you will find a *Life Science Leader* exclusive with Eli Lilly's CFO, Derica Rice (see p. 14), sharing his insights on getting through "years YZ", as well as the experience serving as interim CEO. But in a never previously attempted move, we opted to develop a secondary deep-dive feature involving several members of the company's executive committee, including its CEO John Lechleiter (see p. 18). While history will support that most businesses are well served by following trends, there certainly seem to be times when going against the grain can be a good business idea. We hope you like it.

Life Science Leader
MAY 2016 VOL. 8 NO. 5

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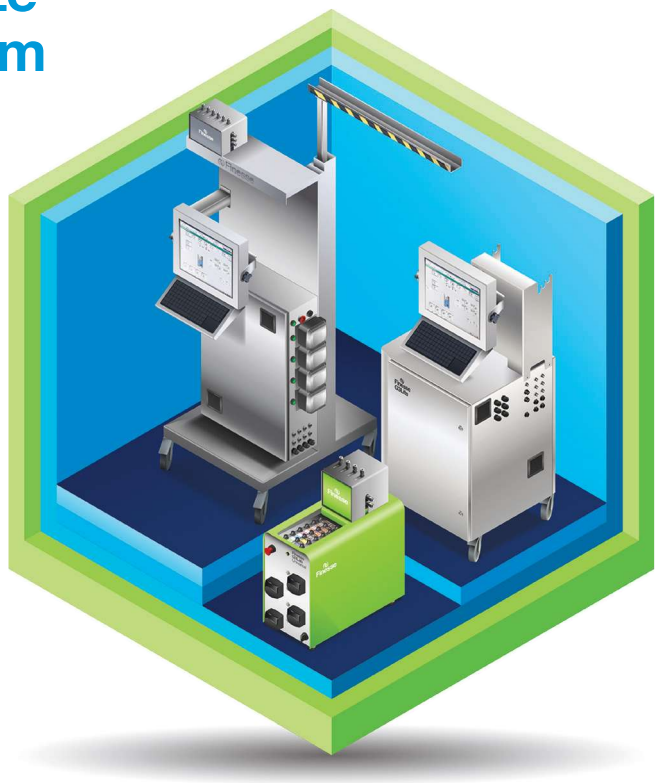

Have a response to our experts' answers?
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Q What are some alternative security solutions to just using a security mark on packaging?

A THIS QUESTION POSES AN INTERESTING DILEMMA to the investments currently directed toward regulations requiring application of unique serialized codes to pharmaceutical packaging. Newton's Third Law reminds us that for every (label security) action there will be an equal and opposite reaction (by counterfeiters). The fakesters won't be denied. They will likely sell unpackaged, bulk pills via secondary channels or attempt to "copy and paste" legitimate bar codes onto falsified labels.

Brand protection experts remind us that multilevel protection is the best safeguard against counterfeits. In addition to package authentication marks, prudent brand owners should invest in markings on the product itself. Despite adding process complexity and cost for manufacturers, ultimately, it's the pill that bears the burden of proving authentication. On-dose technologies such as Raman chemical imaging, micro-taggants, and DNA-like fingerprinting are viable complements to package markings.

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

Q Could a proposal like the RESULT Act end the FDA's monopoly on approving drugs?

A THE RESULT ACT SEEKS TO CHANGE how drugs are approved in the U.S. by allowing for reciprocal approval of drugs, devices, and biologics from foreign sponsors in European countries, Japan, Canada, Israel, and Australia. The bill would allow Congress to overrule FDA rejections of life-saving drugs with a majority vote via a joint resolution. While drug shortages are real, these shortages do not involve novel drugs but rather older generic drugs that are low profit, which manufacturers no longer are willing to produce. Passage of the RESULT Act would not solve this problem.

What this act *would* do is reduce the FDA's authority and relax approval standards to the lowest common denominator. Furthermore, giving Congress the ability to overrule the FDA on drug approvals would make the process more political than scientific. The FDA's role in adjudicating the risk-benefit for any new medicine should not be tampered with.

JOHN LAMATTINA, PH.D.
is the former senior VP at Pfizer, Inc. and president of Pfizer Global Research and Development. In this role, he oversaw the drug discovery and development efforts of more than 12,000 colleagues in the United States, Europe, and Asia.

Q What are some best business practices that make clinical trial participants feel like valued customers?

A I AM NOT CONVINCED WE WANT TRIAL PARTICIPANTS to feel like customers. A customer relationship tends to flow one direction – from seller to buyer. My goal is to have a bidirectional relationship with trial participants where they are sharing insights and data, and I can share information and data back. But I definitely want them to feel valued in that relationship, which I can get closer to realizing by acting on shared insights, being transparent with information, and quite simply – saying thank you. Driving consistency is hard in a large organization and requires appropriate change management to help teams along with clear expectations from company leadership of the importance of demonstrable patient engagement. I recently heard one executive suggest that maybe everyone in the organization needs a goal to sit and talk to at least one patient this year – perhaps that is where we begin.

CRAIG LIPSET
is head of clinical innovation within worldwide R&D at Pfizer. In this role, he works across units and stakeholders to define Pfizer's vision for the future of clinical trials and enables the initiatives and investments to create that future.

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An Exclusive Interview With Stephen Ubl, President Of PhRMA

JOHN McMANUS The McManus Group

JM: You took the helm at PhRMA just as the firestorm over pricing erupted, particularly with the aggressive pricing strategies adopted by Turing and Valeant. Some politicians have tried to capitalize, claiming that Turing's and Valeant's actions are endemic to the pharmaceutical industry. What is PhRMA doing to educate the public and policymakers and correct the narrative?

SU: *As I have said before, Turing and Valeant are essentially hedge funds masquerading as pharmaceutical companies. Yet some have used these isolated examples to advocate for sweeping change in public policies that risk slowing the progress we have made against disease and would delay the development of the next generation of treatments and cures for patients.*

The patient perspective should be front and center in any healthcare policy discussion. This is an exciting time for biopharmaceutical innovation with new medicines that are completely transforming care for patients fighting cancer, hepatitis C, heart disease, and other debilitating ailments. With our "From Hope to Cures" campaign we are hoping to educate policymakers in Washington, D.C., about the positive impact new medicines have on patients and the healthcare system. Too often the debate ends up focusing only on dollars and cents and ignores the patient perspective. Without a better understanding of the value new medicines and treatments provide, we face a greater risk of public policy changes that would inhibit innovation and harm patients.

JM: For years the industry was criticized for producing "me-too" drugs in crowded therapeutic classes. Yet recent transformative cures, like new HCV (hepatitis C virus) products, have been pilloried the most! How much of this anger surrounding the price of these cures is related to the list price and how much is toward the out-of-pocket expenses imposed by health plans?

SU: *Unfortunately, we have seen a rapid rise in the number of health plans with high deductibles for medicines – doubling in just the last three years. For patients with a combined deductible of $2,000, they are faced with paying on average 46 percent of their pharmacy costs out of pocket compared to just 28 percent of their hospital costs. Patient assistance programs sponsored by America's biopharmaceutical research companies are one option to help patients maintain access to needed medicines if they are uninsured or underinsured.*

With that said, focusing solely on the list prices of medicines is misleading because it ignores the significant discounts and rebates negotiated by insurers and pharmacy benefit managers. A new report from the IMS Institute found net prices for brand medicines increased just 2.8 percent in 2015, down from 5.1 percent the prior year as discounts and rebates negotiated by payers rose sharply. Similarly, CVS Health and Express Scripts recently reported actual medicine spending growth in 2015 was less than half from the prior year. This is due to a competitive marketplace for medicines where large, powerful purchasers negotiate aggressively and generic utilization rates are nearly 90 percent.

JM: It seems that some in the PBM (pharmacy benefit manager) industry are fanning the flames on antipharmaceutical rhetoric. They are bemoaning the rise of "specialty medications" and claiming new medicines will bankrupt the healthcare system and wreak financial havoc. What's this really all about?

SU: *Recent comments from PBMs and insurers disprove misleading claims previously made about spending on new innovative medicines. For example, over the past year, payers claimed life-changing treatments and cures for hepatitis C and high cholesterol would bankrupt the healthcare system and wreak financial havoc. Yet Express Scripts, the nation's largest PBM, now touts hepatitis C treatment is less expensive here than in western countries thanks to its aggressive negotiation. And last year it touted it can include both new cholesterol-lowering medicines, called PCSK9 inhibitors, on its national list of covered medicines thanks in part to substantial negotiated discounts. The bottom line is private negotiations between manufacturers and payers drive our competitive marketplace and provide patients with access to a broad range of innovative new treatments and cures.*

JM: Should the pharmaceutical industry adopt a more aggressive approach to PBMs, as the Anthem-Express Scripts litigation has provided a glimpse that patients may not be benefitting from rebates provided to PBMs?

SU: *In the biopharmaceutical market, large, powerful PBMs have the ability to negotiate significant discounts and rebates, establish formularies, and incentivize patients to use lower-cost generic alternatives. In fact, the top three PBMs manage 75 percent of all prescriptions filled.*

At the same time, the introduction of high pharmacy deductibles has led to major changes for patients. In the exchanges created by the ACA, patients often face

"Recent comments from PBMs and insurers disprove misleading claims previously made about spending on new innovative medicines."

STEPHEN UBL

deductibles of $3,000 or more without the benefit of an employer contributing to an HSA to help defray the out-of-pocket costs. Patient assistance programs sponsored by America's biopharmaceutical research companies are one option to help patients maintain access to needed medicines if they are uninsured or underinsured.

Ultimately, private negotiations between manufacturers and payers drive our competitive marketplace and provide patients with access to a broad range of innovative new medicines and foster the development of new treatments and cures patients desperately need.

JM: The Obama administration has proposed a nationwide "experiment" on Medicare Part B physician-administered drugs that would impact three in four Medicare physicians and their patients, many of whom have cancer and other serious ailments. Do you think the administration has properly focused on a "defined population where there are deficits in care leading to poor clinical outcomes" as required by the Center for Medicare and Medicaid Innovation (CMMI) statute for such demonstrations?

SU: *The proposed Medicare Part B payment model marks a dramatic departure from CMMI's usual voluntary testing approach. Mandating broad changes for the majority of Medicare beneficiaries is government overreach.*

This proposal would come between providers and patients by allowing the government to make one-size-fits-all value judgments about the best care for Medicare patients. As new medicines become available, especially new targeted and personalized medicines, like President Jimmy Carter's recent cancer treatment, Medicare physicians and patients should have those options available to them.

Finally, the Medicare Part B payment method is market-based and works well to control costs. Part B spending growth is not driven by prescription medicines, and spending on medicines has remained below medical inflation. Instead, rapid provider consolidation and changes in site of care are driving up costs for patients and Medicare.

JM: We are now seeing state ballot initiatives that would cap pharmaceutical prices to state governments at the level provided to the federal Department of Veterans Affairs. It seems there is very little understanding of the different payer systems — it's like France demanding the Greece price. What is PhRMA's position on these initiatives?

SU: *We have serious concerns about these measures and the potential impacts they will have on patients' access to medicines and future innovation. In California, we are part of a growing coalition of groups opposed to this November 2016 ballot measure because it will negatively impact millions of Californians.*

JM: We've seen the 340B program expand dramatically in just a few short years. A number of government reports have expressed concern about lax oversight and potential abuse of the program. Physician groups have also argued that 340B has fueled provider consolidation and undermined competition. How is the pharmaceutical industry tackling this issue?

SU: *The 340B was created to help vulnerable or uninsured patients access needed prescription medicines. Unfortunately, the program has strayed from its core mission and is growing dramatically, with hospitals responsible for much of the growth — while clinics receiving government grants largely use the program appropriately to improve access to medicines and support the worthy missions described in their grants. Thoughtful reform is needed to ensure the program benefits the patients as was intended. We are committed to working with congress and the administration to address the 340B drug discount program and its market-distorting effects. Core areas of reform include a better patient definition, addressing hospital eligibility criteria, slowing growth of contract pharmacies, curbing provider consolidation, and increasing oversight and accountability in the program.*

JM: How are you trying to reshape PhRMA? What should it stand for or against? Give us a glimpse into how you are trying to execute on that strategy with some hires you've made or priorities you're emphasizing.

SU: *I want my tenure to be marked by PhRMA playing a leadership role in advancing pro-consumer, pragmatic policies that enhance the private market and address costs holistically. PhRMA has been viewed as very effective at defeating bad policies, but I think we can do a better job advancing a set of proactive policies.*

There is a right and a wrong way to find real solutions for America's patients. The wrong way are policies that distort, rather than enhance, the private market such as de facto price controls or importation, and as a practical matter, these ideas have been rejected on a bipartisan basis by agencies like the CBO (Congressional Budget Office) and FDA. Instead we need to concentrate on pragmatic proposals that increase competition, modernize the FDA, remove barriers that limit paying for value, address market-distorting programs like 340B, and empower and engage consumers with information to make better informed healthcare decisions. If we focus on these issues, we can enhance the private market and improve patient access to high-quality, patient-centered care. L

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

Addex Therapeutics

Targeting Parkinson's dyskinesia and other rare CNS disorders with a novel receptor-binding approach.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Addex Therapeutics is in mid-stage development with several CNS-drug candidates, including dipraglurant, in a Phase 3 trial for treating Parkinson's disease levodopa-induced dyskinesia (PD-LID); a Phase 2b/3 of dipraglurant for dystonia; and a Phase 2 proof-of-concept study for ADX71441, an activator of gamma-aminobutyric acid subtype B (GABAB) receptor, in Charcot-Marie-Tooth type 1A neuropathy. Drugs in the Addex portfolio are products of its platform of small molecule allosteric modulators (AMs), which may have advantageous binding properties.

WHAT'S AT STAKE

Medical need, science, and business sometimes intersect, to their mutual benefit. Addex shows how the lucky correlation can happen in a company, even when the enterprise begins in one place and winds up in another. Many of our Companies to Watch start up and stick with the same purpose evidently to the sweet or bitter end. Many others have made chameleonlike changes in their strategic direction and medical purpose, at times many times over. In the case of Addex, several redirections put it on a path to its lead development candidate, dipraglurant, now in Phase 2 trials for dyskinesia and dystonia.

In last month's issue, Dr. Robert Hauser, a key academic/scientific opinion leader at the University of South Florida, bemoaned the lack of effective medicines for levodopa-induced dyskinesia in Parkinson's disease (PD-LID). ("Hot New Therapeutic MoAs Versus Neurodegenerative Diseases, Part Two, Parsing Out Parkinson's," April 2016.) About the same time I interviewed Hauser, I met Tim Dyer, CEO of Addex, at the BIO CEO & Investor conference in New York. When I was unable to work Addex into the Parkinson's article, I vowed to cover it in this column.

But of course, I found out the company is about much more than one product. Behind the product is a new platform already producing additional candidates. Dipraglurant is the first of multiple small molecule AMs in the Addex pipeline. AMs are drugs that bind with a receptor at a site other than the so-called active site most other drugs target. The AM drug thus avoids competition with ligands that bind to the active site; it binds to another site where it can regulate the disease-related receptor up or down, even when natural ligands fully bind to the active one. (Negative or down-regulating AMs are NAMs; positive or up-regulating, PAMs.) Addex posits AMs will thereby have better binding rates than non-AM drugs.

So, if AMs have such therapeutic advantages over conventional drugs, what barriers have kept other companies from exploiting them — and how does the Addex technology overcome those barriers? "The main barriers are the screening tools to discover AMs and support their chemical optimization," explains Dyer. "In 2003, when Addex pivoted to focus on AMs, we developed a proprietary in vitro pharmacology screening platform designed to specifically identify AMs. This is a significant competitive advantage."

Dyer and several partners founded the company in 2002, initially to pursue medicines to treat drug addiction, but a year later it shifted to developing the AM platform and CNS portfolio, beginning with dipraglurant, a NAM targeting mGluRs (metabotropic glutamate receptors) in rare movement disorders. Addex considers itself undervalued, and Dyer indicates plans are underway for a $30 million PIPE (private investment in public equity) to fund its dipraglurant Phase 3 trial in PD-LID and Phase 2b/3 in dystonia, as well as a Phase 2 with its candidate in Charcot-Marie-Tooth neuropathy. In applying its AM platform, it appears to have chosen its lead candidates and indications wisely, based on the intersection of medical need, science, and — so far, but with mountains yet to climb — business. L

TIM DYER CEO

Vital Statistics

8
Employees

Headquarters
Geneva, Switzerland

Finances

Total raised (SFr280M)
$229M

VCs (SFr106M)
$81M

IPO (SFr137M)
$111M

PIPEs (private investment in public equity) (SFr37M)
$37M

Research Partnership Funding

Janssen Pharmaceuticals, CNS disorders, currently epilepsy €10.2M ($11.7M) to date; potential €109M ($124.6M) milestones, royalties

Pierre Fabre Pharmaceuticals, CNS research

Other Partners

Michael J. Fox Foundation: grant funding ($1.9M to date)

Dystonia Medical Research Foundation: clinical trial design

National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Drug Abuse (NIDA)

Latest Updates

December 2015: Swiss government grants more than $1.03M (SFr1M [Swiss franc]) to research programs with Universities of Geneva and Lausanne

January 2016: FDA orphan drug designation for dipraglurant in PD-LID

January 2015: Phase 2 dipraglurant study shows significant anti-dyskinetic effect in PD-LID

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Why Lilly's Derica Rice Isn't Your Typical CFO

ROB WRIGHT Chief Editor @RFWrightLSL

Derica Rice isn't what I expected.

Honestly, not having interviewed many pharma company CFOs, I wasn't sure *what* to expect. However, from the little I did know about Rice, the CFO of Eli Lilly and Company, I knew that an in-depth discussion of complex financial strategies or the kinds of detailed analyses found only in a company's annual report wasn't what I hoped he'd talk about. I wanted to know more about what it takes to be a CFO in this industry these days. What kinds of decisions is he faced with? What business strategies does he struggle with, and how does he overcome the challenges of this demanding position? Basically, I wanted to know what made this guy tick. Luckily, he didn't disappoint.

An Unusual Tenure

There are a few facts about Rice that are not only atypical of a Big Pharma CFO but also warrant further exploration. First, he has spent his entire professional career — 26 years — at Lilly, including a role as a pharma rep. "I remember meeting Jim Cornelius [Lilly's CFO from 1983 to 1995] back in 1990 when I was interviewing, but at the time I really didn't know what a CFO did," Rice says with a chuckle. Those days in field sales may be long in his past, but his experiences during that time forged an appreciation for this business function that he still cultivates in his current role. For example, he occasionally will go on territory field visits and even attend field sales meetings. "To understand the daily challenges they are facing, I need to hear what is on their minds," he says. "If, as a senior leader, you take the approach that you don't have time or are too important for a field sales ride along, not only are you missing the challenges and problems that are out there, but you also will be blind to many emerging opportunities." But it's not just the field group that he stays connected with; he spends time with the R&D team, talking to Lilly scientists and learning what they are trying to accomplish — and what he can do to help.

Another fact about Rice that makes him unique in this industry is also tied to his tenure at Lilly. His 10-year run as CFO outpaces the average tenure of a CFO at a Fortune 500 company by four years. That's impressive on its own, but it's even more significant when you consider that he's held this position without having an accounting background. Oh, and don't forget that he has served on Lilly's executive committee longer than all but one of his leadership peers — only CEO John Lechleiter has served longer. In fact, it was a meeting with Lechleiter in early 2013 that led to one of the most unusual and interesting facts about Rice.

An Unexpected Challenge

As Rice recalls, the one-on-one meeting had been scheduled well in advance, so it wasn't unexpected. The company had just closed the books on 2012, a year punctuated by declines in just about every key financial performance metric except for how much it had spent on R&D (see table 1), so the CFO obviously had a lot on his mind.

"I walked into his office with my typical to-do list," Rice recalls. "As I got through bullet points one and two, I could see John was becoming a little impatient." Undeterred, Rice continued his review. After a few more minutes Lechleiter interrupted and said, "That's not what I need to talk to you about today." The CEO then explained that he needed to have surgery for a dilated aorta. "He was very matter of fact about letting me know that he was going to be out for a while," Rice states. "But when he said that he wanted me to step in and serve as interim CEO, I heard the words, but at the same time … I didn't. It was a lot to process."

To an outsider, the decision probably seemed logical. After all, Rice was a long-time Lilly employee and even had been CFO for the two years prior to Lechleiter being named CEO (see "Different Leaders Face Different Challenges"). Naming him interim CEO was also in accordance with the company's bylaws, so it really shouldn't have been a surprise that the board of directors agreed to the then 48-year-old Rice serving as interim CEO.

Still, in that moment, Rice's mind was awash in the enormity of this news. "You have to understand; I grew up in Decatur, AL, with very modest means," he reflects. "We weren't poor. We were *po*. The difference between poor and po is that when you are po, you are so poor you can't even afford the last o and r!" The oldest of seven whose father died of a stroke when Rice was just 11, he and his siblings were raised by his mother, a type 2 diabetic who provided for the family by working as a school custodian.

He says those humble beginnings have helped him stay grounded during his career, which is a personality trait that is especially useful when you've been suddenly tapped to be the CEO of a 140-year-old pharma giant — even if it was for only 68 days. But Lechleiter and the board's faith in Rice during this time indicates the kind of versatility that a pharma CFO needs to exemplify these days. In other words, the job goes well beyond that of merely directing corporate fiscal functions.

Preparing For Years YZ

Beyond his field sales experience, Rice served in various management positions

TABLE 1: 10 YEARS OF ELI LILLY & CO. KEY PERFORMANCE MEASURES

	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004
Revenue	$19,615.60	$23,113.10	$22,603.40	$24,286.50	$23,076.00	$21,836.00	$20,371.90	$18,663.50	$15,691.00	$14,645.30	$13,857.90
R&D	$4,733.60	$5,531.30	$5,278.10	$5,020.80	$4,884.20	$4,326.50	$3,840.90	$3,486.70	$3,129.30	$3,025.50	$2,691.10
R&D as % of Revenue	24.13%	23.93%	23.35%	20.67%	21.17%	19.81%	18.85%	18.68%	19.94%	20.66%	19.42%
Net Income	$2,390.50	$4,684.80	$4,088.60	$4,347.70	$5,069.50	$4,328.80	-$2,071.90	$2,953.00	$2,662.70	$1,979.60	$1,810.10
EPS	$2.23	$4.32	$3.66	$3.90	$4.58	$3.94	-$1.89	$2.71	$2.45	$1.82	$1.67
Employees	39,138	37,925	38,350	38,080	38,350	40,360	40,450	40,600	41,500	42,600	44,500

(Dollars in millions, except per-share and employee data)

The Employee Challenges Of A Looming Patent Cliff

The patent loss time period spanning 2011 – 2014 was referred to at Lilly as "years YZ." Though the dreaded patent cliff would hit the balance sheets of many big pharmaceutical companies, the reality is that Lilly was due to be one of the hardest hit. "When I became CFO in 2006, the initial crux of my job was to begin cultivating plans and strategies for how we would manage our way through years YZ," explains Derica Rice, Lilly's CFO.

The first challenge was to get the organization to pay attention to a series of events that wouldn't take place for another three to five years. That was especially difficult considering that in 2007 the financial forecast for Lilly looked pretty favorable, having just closed the books on its best year ever (i.e., $3 billion increase in annual revenue). But Rice and CEO John Lechleiter knew that preparing for the pending storm would require more than 6 to 12 months of preparation. "It would take years to put things in motion," Rice attests.

The second challenge was to prevent employees from losing sight of the present. "We still needed good performance in the near term," Rice says. "Though you are trying to get the 'pending storm' message to resonate, you don't want people running for shelter three years too early."

that helped give him the versatility he would later need as CFO. For example, in 2004 he was the head of the company's global planning organization when a generic manufacturer challenged the patent validity of Lilly's Zyprexa (olanzapine), an antipsychotic generating $2.5 billion annually at its peak, that wouldn't go off patent until 2011. "My job was to put together a contingency plan in case we prematurely lost the patent," he explains.

Though Lilly was successful in upholding its patent, the experience gained from the planning process proved very fruitful. Rice says it helped the company determine what elements of the business Lilly would want to leverage in order to endure such a patent expiration scenario. In particular, this meant pursuing an innovation-based strategy.

The patent loss time period spanning 2011 to 2014 was referred to at Lilly as "years YZ." When Rice took over as CFO in 2006, he was immediately thrust into solving the problem of how to survive *and prosper* throughout those years. "We decided to double down on investing in R&D," recounts Rice. "We weren't going to do large-scale mergers to finance and engineer our way through such a scenario. We weren't going to diversify into noncore biopharma areas such as consumer products or generics. And, we weren't going to cut R&D spending by 30 or 50 percent as a means of financially traversing the anticipated revenue gap."

He explains that the plan was to figure out how to improve R&D productivity and quality, increase pipeline output, and then rebase (i.e., improve and reduce Lilly's cost structure) the company. "We wanted to take the hits from the patent expirations but then begin growing the company, albeit off a smaller starting base." (As table 1 illustrates, Lilly consistently increased investment in R&D, as either a dollar amount or as a percentage of revenue.)

Decision Making Amidst The Noise Of Naysayers

Of course, when you're talking about the financial strategies of a publicly traded pharmaceutical company, you're bound to be inundated with naysayers. Indeed, when Lilly first announced its R&D philosophy, there was an abundance of outsiders who were quick to second-guess this strategy. Rice says that skepticism only fueled the company's desire to further validate whether this was the right path for Lilly. "We didn't discount those opposing thoughts, views, and comments; we fully considered them," he says.

Rice and the executive team looked across the industry for examples of companies having successfully managed their way through this type of serious patent expiration without taking "some fairly draconian action, including changing their strategy." Other companies had chosen to go the M&A route. For example, shortly after Lilly announced its R&D strategy, Pfizer purchased Wyeth. About a month later, Merck said it was acquiring Schering-Plough. "A lot of our management team felt that Merck and Lilly were very similar in our commitment to R&D, and here they were choosing a very different route than what we'd chosen. Then, another of our competitors announced they were cutting R&D by 20 percent," Rice adds. "Still, I can't say that we second-guessed our decision."

The company did a lot of contingency planning during this time. Rice says the goal wasn't to confirm that they were right about their decision but to determine how wrong Lilly could be and still be OK. "The goal was never perfection, because trying to put together the perfect plan would be a flaw in and of itself," he says. Throughout the contingency planning and testing, the one fact that consistently became apparent was the

overwhelming importance of R&D over the years to the company's success. "With every challenge we have faced — whether it was Oraflex [Lilly's arthritis drug linked to toxic reactions in the 1980s], Clinton administration healthcare reform, or product patent expiration — it was our R&D innovation and our ability to bring new clinically differentiated products to market that brought us through these tough times. We decided that was something to focus on since it was within our control."

How A CFO Drives Company Focus

As CFO at the time, Rice's role was to drive that focus and prioritization and help the company navigate the trade-offs that are inevitable with such a plan. For example, all of the company's business segments were narrowed down to five — bio-medicines, diabetes, animal health, emerging markets, and oncology. From there, the company looked at the human health therapeutic areas that seemed to have the best opportunity (e.g., neurodegeneration, oncology, diabetes, autoimmune, pain). "We then built our R&D efforts on these, determining which specific molecules within each therapeutic category we wanted to pursue," he explains. "We had to determine how we would resource these molecules, and for those not selected, decide if we were going to shelve them for later or discharge them altogether."

Rice admits that getting through the YZ period required a great deal of discipline from himself and the entire leadership team. After all, despite all their planning, not everything went off without a hitch. When they started the YZ race, eight of the first nine late-stage molecules in their pipeline failed. "It was a bit of a surprise that not only taught us about our level of determination but also the importance of execution, the need for continuous improvement, and that getting through all of it would require the entire team," he states.

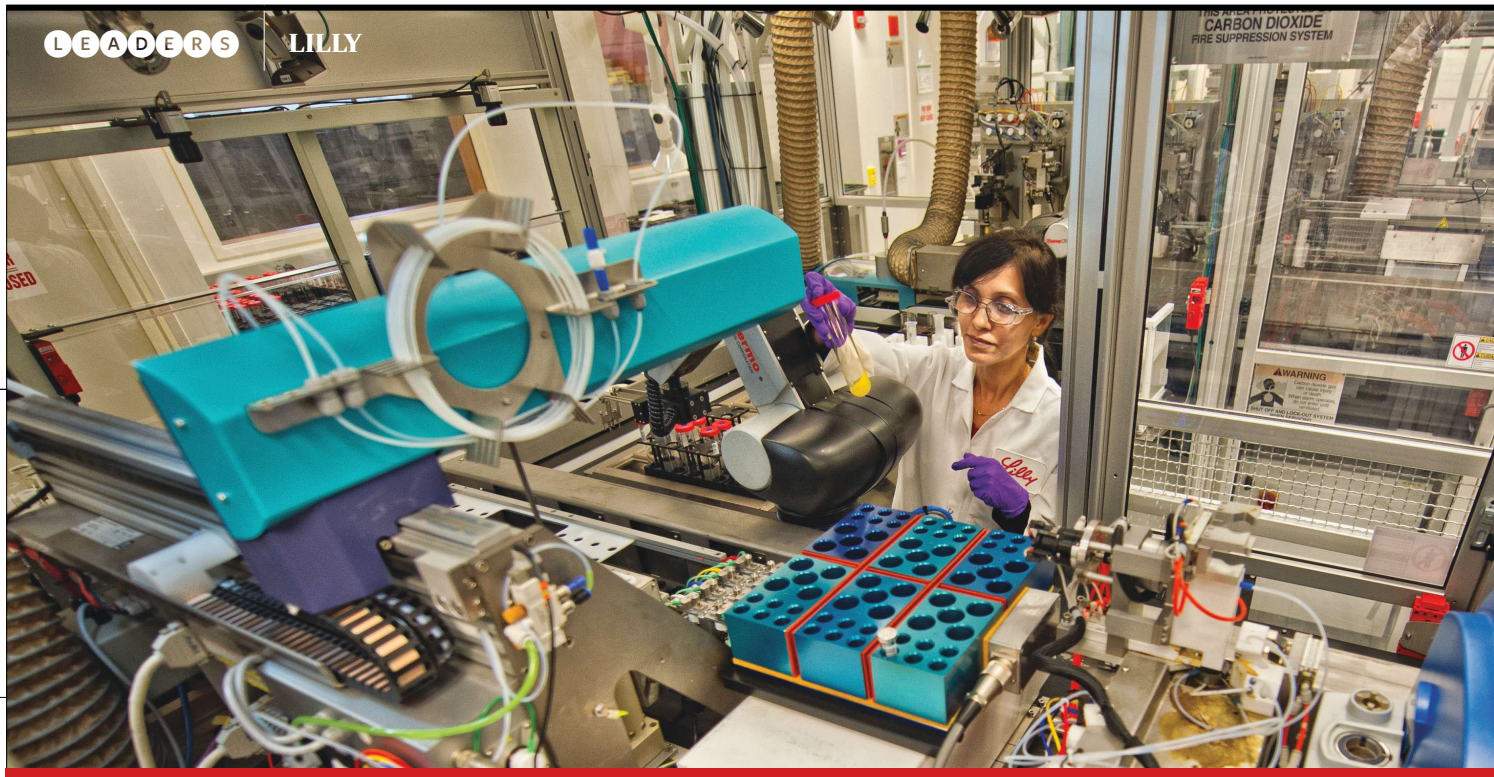
Rice may not be your typical pharma CFO, but I'm guessing Lilly's long-term investors are OK with that. The road is littered with carcasses of companies that took "typical" approaches to hiring leaders and solving problems. Sometimes success resides in atypical leadership. L

Different Leaders Face Different Challenges

When Derica Rice was named CFO of Lilly in 2006, he joined John Lechleiter as a member of the executive committee. At the time, Lechleiter was functioning as the company's COO. But this wasn't the first time the two had worked together. "I had the opportunity to work with John before he became the COO," Rice explains. "When he was the president of our global pharmaceutical business and head of what we used to refer to as our product teams, I was his CFO. It was then that I really got a sense of his approach, philosophies, and leadership style." While this may have been Rice's first opportunity to work closely with the CEO, as it turned out, it wouldn't be his last.

History has shown that turnover at the CEO position at many companies often doesn't bode well for other members of the senior leadership team. But when Lechleiter replaced Sidney Taurel as CEO in 2008, one of the constants through the transition was Rice. Being one of the few Lilly executive committee members to have served in his current position under both CEOs, Rice has a rather unique perspective on both leaders, as well as the challenges each faced. "As you can imagine, their styles were very different, and that's to be expected," he says. "But the business circumstances were also very different. When Sidney [Taurel] was in the role, we had come on the heels of the Prozac [fluoxetine] patent expiration." The blockbuster antidepressant that was first launched in early 1988 received numerous additional indications that extended its patent into 2001. As a result, the extremely successful selective serotonin reuptake inhibitor (SSRI) ended up generating approximately 30 percent of Lilly's total revenue during its life span. "We had launched a series of new products under Taurel, and the company had gotten to a pretty good growth trajectory," Rice reflects. "But as John was looking to take on the role of CEO, he wasn't facing the patent loss of one product but four of our largest products representing about 40 percent of our revenue."

The antipsychotic Zyprexa (olanzapine), generating $2.5 billion annually at its peak, would go off patent in 2011. In 2013 the company faced the loss of not one but two drugs (i.e., Humalog [insulin lispro injection] and Cymbalta [duloxetine]) with a combined annual revenue of $7.4 billion. Finally, in 2014 Lilly would lose the $1 billion revenue generated by its osteoporosis treatment, Evista (raloxifene). "How do you lead a company through such a series of patent expirations, rebuilding that base, and still continue to have an ongoing entity?" Rice asks. "It required a different leadership style, approach, and focus."



LILLY LIVES ON *And Prospers*

At 140 years, setting the industry benchmark for constancy and growth

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Eli Lilly and Company last appeared in these pages just short of two years ago, in a story based on our conversation with chairman, president, and CEO John Lechleiter — "Lilly's Tale of Trial and Tenacity" (June 2014). At the time, the company faced many doubts, and more than a few loud doubters, concerning its struggles to overcome patent expirations for its most lucrative products. Each time it encountered a setback in clinical trials, the predictable swarm of tweets, trade news, and commentaries derided Lilly as a lackluster performer. Now, the critics seem quieter as the company points to big changes and achievements in the past two years.

That is one reason we return to visit the company again, this time in an expanded form, featuring not only Lechleiter but also a group of top executives leading its two largest businesses, Bio-Medicines and Diabetes, plus critical functions for Lilly as a whole, manufacturing and quality. Coincidentally, our multifaceted update comes in the context of Lilly's history of 140 years — an extraordinary life span for a U.S. company, perhaps due to the company's constancy in culture and mission. For Lilly appears to have achieved what a number of other Big Pharmas have not — global-scale growth in value without reliance on repeated M&As.

Starting with Lechleiter's update on the company overall, we look at each of the organizations headed by the following: David Ricks, president of Lilly Bio-Medicines; Enrique Conterno, president of Lilly Diabetes; Maria Crowe, president, Manufacturing Operations; and Fionnuala Walsh, senior vice president, Global Quality. In a separate article, our chief editor Rob Wright writes about the critical role of Lilly's chief financial officer, Derica Rice. Throughout this expanded feature runs a unifying theme: how corporate continuity complements corporate change.

HISTORY MADE *Now*

A meaningful review of the past should shed light on the present. As Lilly celebrates its 140th birthday, it has a natural reason to look back to its beginnings for a proper perspective on its current state. In 1876, the company's namesake and founder, Eli Lilly, opened a lab to produce reliable, high-quality medicines he found lacking in his Civil War experience and afterward in the country in general.

A practicing pharmacist before the war, Lilly assembled and led his own company, holding the rank of colonel in the Union Army. He saw plenty of death, injury, and disease during his time in combat and as a prisoner, usually in the worst of conditions for medical care and supply. But the state of medicinals across the expanding nation was not much better once the war ended; people had no way of confirming who made them or what was in them. Lilly eventually hatched the idea for a new kind of pharmaceutical supplier placed in the heart of the Midwest — one that would adhere to superior quality standards and help drive the development of prescribing by physicians. From that little acorn, initially a tiny family enterprise, the great oak of the Lilly company has grown.

John Lechleiter, a "Lilly history wonk" by his own description, takes up the story in the 20th century, with a seismic event that changed the company's course for then, now, and into the future. "An ambitious and capable research director with Lilly at the time, Dr. George Clowes, got on a train Christmas Day in 1921 and traveled from Indianapolis to Connecticut to hear Frederick Banting of the University of Toronto present a paper at the American Physiological Society on the discovery of insulin. Clowes then began to urge Banting, his assistant Charles Best, and his boss John Macleod into collaborating with Lilly."

The company consummated the insulin deal with the University of Toronto in May 1922, with Colonel Lilly's grandson and namesake, Eli Lilly, then-CEO, signing. Banting and Macleod won the Nobel Prize for Physiology or Medicine in 1923 for their insulin discovery.

"That deal brought the company into the modern era," says Lechleiter. "When we launched insulin in 1923, it was literally a life-saving drug, and it has since stood the test of time. Unfortunately, diabetes remains unconquered, and we still need insulin today. It's Lilly's largest single business after 100 years. But I believe the decision to supply insulin commercially typified our willingness to take risks, coupled with scientific excellence as embodied in Clowes, who recognized what an opportunity this presented and then applied his doggedness and determination."

The company's original business model — creating a high-quality standard for all pharmaceuticals — guided many of its actions in setting up the development and production of insulin, then refined from animal pancreases by methods the company invented to ensure purity and batch consistency. Long before FDA regulations existed, Lilly did clinical testing in 1922 and 1923 to ensure that, when it launched the product, it could tell physicians how to use it. Eventually, going beyond its own internal initiatives, Lilly would play a leading role in establishing the FDA and its regulatory authority.

Lechleiter cites the next formative event for the company, still relevant today: the development of its expertise in drug fermentation, beginning with penicillin production in the 1940s. Lilly also used a fermentation process to produce more than half of the Salk polio vaccine for U.S. children in the mid-1950s. "The fermentation capability enabled us to discover and produce molecules such as vancomycin, still today one of the last lines of resistance against MRSA; erythromycin, another Lilly discovery in the 1950s; and the cephalosporin family. Our fermentation capability also carried over to our partnership with Genentech in the late 1970s to develop biosynthetic human insulin," he says.

Biosynthetic insulin was an event in itself. When Lilly and Genentech launched Humalog in 1983, it was the first biotech therapeutic ever approved — not only a first in technology but also the beginning of an entire industry sector whose legacy endures. "It is still fermentation technology that enables us to make all of our biotech products," says Lechleiter.

The fourth transformative historical event for Lilly, he believes, was its introduction of Prozac (fluoxetine), the world's first serotonin-uptake inhibitor for depression — both for the impact Prozac had on the company and also for

JOHN C. LECHLEITER, PH.D.
Chairman, President, and CEO

the huge impact it had on the treatment of the condition, largely bringing mental illness out of the closet. "With biosynthetic insulin and Prozac in the 1980s, the company began to move beyond antibiotics and animal-insulin and into biotechnology and neuroscience as key areas of growth, which they continue to be today."

Lilly's current neuroscience pipeline is mainly focused on neurodegenerative diseases and pain, and the biggest news generator there is its drug for Alzheimer's disease, solanezumab, an anti-amyloid plaque antibody. (See also the sidebar, "Tracks of Growth," and the section, "Therapeutic Transformations.") Lechleiter sees the challenge of developing the treatment as a long haul. "We have been working in Alzheimer's for 27 years. We've had ups and downs, mostly downs, but we have made progress. We worked on Prozac and research related to Prozac from the 1950s through the 1970s."

Sharing Value

Lechleiter asks rhetorically, "How do you sustain that kind of investment over such a long period of time?" He answers, "You can only do it if you have the promise of being rewarded for the risk that you take. We reward risk-taking in the United States with free pricing, which of course the company must do responsibly."

Lilly competes on price to some extent, meaning its price points for any key product take into account the relative pricing of comparable agents from other companies in the same class. Therapeutic "equivalence," where meds with different mechanisms for the same indication must compete against each other in formulary selection, widens the competitive field, as Lechleiter notes: "There is no product of ours out there today that doesn't have a competitor." He has cited a range of discounts from the company's average list prices of up to 33 percent for commercial health plans and 81 percent for government payers.

"It is not just price, but price is certainly a lever, and sometimes you have to offer a discount or a rebate for pharmaceuticals as you would in other industries and markets. It's not a perfect market, but it's a better market than most people believe it is."

So, does pricing moderation compromise shareholder value — or enhance it? In Lilly's case, a theoretical answer may not be relevant, because the numbers speak louder; whatever the company is doing, the results look positive. Since the industry's nadir in 2009, Lilly has boosted shareholder return by about 225 percent, or about 125 percent more than the average of its peer group. Of the top 12 pharma companies in total shareholder return, Lilly is now the third company on the list, leading much larger companies such as Pfizer, Novartis, and Merck. Of interest, Lilly stands only in the midteens among the top pharma companies by sales.

"Shareholder value follows from all the things that you do, and in our industry, it's all about creating value through your pipeline," says Lechleiter. "Now, when I look at our pipeline chart, I see lots of positive data readouts. Ultimately, that's what sets the candidates apart."

Lechleiter still believes a major source of value for Lilly and its shareholders is that the company has not been distracted by major mergers and acquisitions. "By

TRACKS OF GROWTH

Lilly's Chairman, President, and CEO, John Lechleiter, discusses some of the main drivers he is counting on to keep the company on track to meet its promised performance goals in 2018. Lilly's two largest businesses are Bio-Medicines and Diabetes, and Lechleiter highlights some of the outstanding new products they have launched and are developing:

"With our approvals last year, we now have in diabetes the most complete product lineup in the industry," he says. "We have one or more molecules in every major class of diabetes medicines, which is unique, and of course partly due to the Boehringer Ingelheim partnership established five years ago. In Bio-Medicines, this year we will complete the transformation from psychiatric drugs, bone health, and men's health into neurodegenerative disease, pain, and immunology. We are now launching Taltz (ixekizumab), our anti-IL17 antibody for treating psoriasis, which is a major event that marks the transformation of Bio-Medicines from a big primary care-focused business to a specialty-care business focused on those three main areas."

In Alzheimer's drug development at Lilly, most of the attention has gone to its anti-amyloid drugs solanezumab and a BACE inhibitor partnered with AstraZeneca (AZ). It also has a PEG-based antibody in Phase 1 that may have a different mechanism for eliminating amyloid from the body. Lechleiter also points to other Alzheimer's approaches in the works. (See more in "Therapeutic Transformations," with David Ricks, president of Lilly Bio-Medicines.)

"We're not just focused on amyloid plaque, but we're also looking at tau." Lilly has a tau imaging agent in Phase 3 and has been investigating anti-tau drug candidates in early-stage research.

An up-and-coming growth driver, Lilly Oncology launched several new products in 2015 and may introduce as many as five others in the next five years. Two of the leading oncology molecules originated at ImClone, which Lilly acquired in 2008: Cyramza (ramucirumab), now approved for four different indications; and Portrazza (necitumumab), approved in 2015 for squamous cell lung cancer. A third Lilly oncology compound, olaratumab, is now under FDA review for treatment of soft tissue sarcoma. An immuno-oncology collaboration with AstraZeneca will test various combinations of AZ's checkpoint blockers with Lilly's pipeline of mainly pathway inhibitors and antigen-specific antibodies.

pursuing our own course, we are creating value for all of our stakeholders. You can expect Lilly will continue to make robust but appropriate investments in R&D and do more preclinical and early clinical-stage deals. But we already have great opportunities to take leadership positions in our therapeutic areas of focus, based on the molecules we have on the market today and the ones we anticipate launching."

Markers Of Progress

Since we last featured Lilly in these pages, the company has been busy living up to its own expectations — reaching goals or markers by which outsiders can judge its post-YZ (i.e., the patent loss time period spanning 2011 to 2014) recovery and growth. In 2009, the company issued a guidance listing four strategies it would employ as it launched new products and reorganized itself into the business-unit structure: grow revenue, expand margins, sustain flow of innovation, and deploy capital to create value. As it gave projections of revenue, income, and cash flow, it promised to maintain its annual dividend and "invest robustly" in R&D. It also pledged to reduce operating expenses to less than 50 percent of revenue by 2018.

To no one's surprise, the company cut jobs and closed facilities to keep that promise. But it also performed a major upgrade on its insulin plant in Indianapolis. Our exchanges with Maria Crowe and Fionnuala Walsh, covered in the following pages, are especially relevant to changes in a critical component of operations: manufacturing.

But cost-cutting and efficient infrastructure have not been the only avenues to reducing OPEX; boosting revenue and margins has had a complementary effect. As revenue grew by almost five percent in 2015, OPEX fell to 54.7 percent of revenue, from 57.3 percent the year before. In January 2015, the company announced it was on track to meet the guidance goals, and it emphatically reaffirmed its progress this year. "Essentially, we have a fixed asset base into which we're launching new products," says Lechleiter. "We're really leveraging our investment in OPEX with all those launches." Lilly has brought eight new products to the market since 2014.

In addition to the financial progress, the launches speak to how well Lilly is fulfilling its third pledge: to sustain the flow of innovation. That includes its R&D investments internally and externally, reflecting the fourth and final pledge — to deploy capital to achieve its objectives, while returning excess cash to shareholders through dividend and share repurchase. "What I've been talking about for the last year or so is basically about how well we are keeping those four commitments," Lechleiter says, "and they will guide us, I'm sure, for another four or five years."

Coming back to how the past informs the present — Lechleiter paraphrases William Ford, great-grandson of Henry, on Ford Motor's 100th anniversary in 2003: "Bill said something like, 'We're happy to celebrate our history, but we're even more excited about creating new history.' At Lilly, we look back with a great deal of pride to our history, and we find relevance in it — it's not just dusty old volumes in a bookcase. Because of that history, we understand better why we are what we are today. We still hold to the values the Lilly family articulated, and lived, in the first 100 years of the company when they were involved, so our history is very relevant to us. But our goal is to take what we have learned from our past and build a brighter future for the company."

In the following, we look more closely at the Lilly organization's striving to apply the constancy of its corporate history and values to the ongoing challenge of necessary change in each of their areas.

MIDDLE EARTH – PRESSURES FROM OUTSIDE

With confidence in the internal workings of his company, Lilly CEO John Lechleiter still engages with many forces beyond any company's control, though perhaps not beyond its influence. Government policy and payer pushback, in that order, top his list of external pressures:

"I believe in policies that encourage investment and innovation – whether in pricing, taxes, or intellectual property protection. Those are critical to how we operate in the world, not just in the United States. We need to speak up and support policies that enable us to address some of the vexing medical problems that remain. Ultimately, the U.S. industry continues to be the world leader in generating new treatments and, in many cases, new cures. It is incumbent upon the leadership of the industry to ensure that we have a voice in the public debates over matters that directly determine whether we can continue to apply the wonderful science emerging in this field."

Included in the same concerns is preserving the unique relationship the U.S. industry has with the government through the world-leading NIH. Lechleiter is optimistic about the long-term survival of the institution and grateful for a last-minute funding boost it received in the most recent budget. But he notes the downward budgeting trend in general:

"The NIH budget peaked in constant dollars around 2003. This industry depends on the basic research funding, that only the NIH can really provide, to enable us to understand biological pathways better and find new therapeutic targets."

Payers have consolidated and comingled with pharmacy benefits managers, and some say they have grown into bullies who put patients and pharma companies at a financial disadvantage. Lechleiter expects other market forces to intervene.

"Third-party payers and PBMs (pharmacy benefit managers) don't exist in a vacuum, and ultimately, for commercial plans, by and large employers determine what the benefits must be, and there are limits to what they would deny their employees. The voice of consumers still shines through here; there are no smarter or better-informed consumers in the world than American consumers. I don't believe that somehow they will be disintermediated by a third party."

THERAPEUTIC *Transformations*

Lilly has defined several of its core businesses mainly by the therapeutic areas each covers. Lilly Bio-Medicines has marketed products in neuroscience, cardiovascular, urology, musculoskeletal, and autoimmunity. Its development pipeline concentrates mainly on neurodegenerative disease, pain, and immunology. David Ricks has done some thinking about the origins of Bio-Medicines, which he heads as president, and he sees much of the company's heritage and traditions as built-in fundamentals of the business he leads.

"Everyone recognizes technology and science as the sources of our growth and improvements for patients. Our success with insulin and antibiotics led to the neuroscience and post-Prozac era, where we professionalized and ramped up research tremendously. We also share a strong commitment to leadership development — bringing up strong leaders from within the company."

For the first century of the company, three generations of the Lilly family led from the top. But family involvement ended after the death of Eli Lilly, Jr., eldest grandson of the founder, in the 1950s, and it became common for the CEOs and other top executives to spend large parts of their careers at Lilly working their way up. At the same time, Ricks notes, many Lilly alumni went on to join the executive teams of other leading industry companies. Ricks came to Lilly in 1996 and rose through the ranks mainly in sales and marketing. He formerly headed the company's China subsidiary and is past president of Lilly USA, becoming head of Lilly Bio-Medicines in 2009.

In his view, a fundamental advantage for the company is yet another inheritance from the Lilly family. "They gave us a commitment to a culture based on the core values of compassion and respect for people, excellence — our slogan is take what you find and make it better and better — integrity in speech and word, and quality in our products and processes."

Leading With Neuroscience

Although the name of the business is Lilly Bio-Medicines, Ricks says the intention was not to make it responsible for all of the company's biologically produced medicines. Two of the other business units, Diabetes and Oncology, are dedicated to single therapeutic areas, so the bioengineered products within those areas are theirs.

"We used the word 'biomedicines' to talk about where the technology was going, because even outside of diabetes, we were mainly capitalizing on biotechnology to invent our way to the next version of Lilly," Ricks says. "That was the challenge we faced in 2009: With the cupboard bare, we would be losing close to $10 billion in revenue due to expired patents during the following four years. And as it turns out, the majority of the company's pipeline now consists of biologics, and in my group, all but one of our late-stage projects are biologics."

Bio-Medicines does have a defined therapeutic focus, however, which is now narrowing and realigning in drug development to neurodegenerative disease, pain, and immunology. Of the highest priority in its pipeline is the Alzheimer's program led by solanezumab.

"Alzheimer's has been a tough and difficult field, really a graveyard of drug discovery," says Ricks. "We have yet to produce a product. In that sense you could say, 'What a disaster.' But as in all science, learning and capability-building are incremental."

In solanezumab's first two Phase 3 trials, EXPEDITION (Effect of LY2062430 on the Progression of Alzheimer's disease) 1 and 2, tested the drug in Alzheimer's patients with mild to moderate disease, many of them possibly at a point when neuron loss was so profound no amount of amyloid plaque removal could likely improve function. But the latest Phase 3, EXPEDITION 3, will focus testing on early-stage patients, based on small improvements shown in an early-stage subset of the EXPEDITION 2 population. Amyloid-theory proponents already feel vindicated by those results, which they believe prove the concept. But of course, FDA approval of solanezumab would hinge on its final Phase 3 safety and efficacy data.

Meanwhile, Lilly Bio-Medicines is backing its bets on the early-stage anti-amyloid approach with additional research. It is working with an NIH-backed academic consortium on the *Alzheimer's Disease Cooperative Study* of people who are still asymptomatic even though their brains show evidence of amyloid accumulation.

Ricks compares the solanezumab situation with a more absolute case of failure in a Phase 3 trial of a cardiovascular drug, evacetrapib, for heart disease prevention in mid-2015. Evacetrapib also took a novel therapeutic approach with a higher than usual risk profile, though Phase 2 data was encouraging. But in Phase 3, although the drug appeared to reduce cholesterol — historically, a reliable biomarker — it did not seem to improve disease outcomes, and Lilly canceled the program. The lesson? Given the still-mysterious nature of the human body, and uncertainties in even the best science, reaching for a medical breakthrough requires taking a high risk.

"When you go into an innovative project, you must have a great deal of conviction that it is a good idea, and if it works, it can be a very significant asset for the company," Ricks says. "A company of our size has to make those bets — not with the whole portfolio because then you put your sustainability at risk — but in challenging areas of science where, if the approach works, it makes a big difference. That is what we're here to do, to solve bigger problems, and Alzheimer's certainly fits into that category."

Bio-Medicines is also fulfilling a commitment made in 2008 to return to immunology, as it develops a portfolio to treat chronic, disabling autoimmune diseases such as rheumatoid arthritis, lupus, and psoriasis. Two late-stage assets lead the immunology pipeline: ixekizumab, which the business hopes to launch soon in psoriasis; and baricitinib for rheuma-

DAVID RICKS
President, Lilly Bio-Medicines

toid arthritis. A growing pipeline of early-to-midstage products looms behind the two leading candidates.

Bio-Medicines is also seeking to "leverage" its biotechnology capability in chronic-pain treatment, a sub-area of the neuroscience pipeline. It has two Phase 3 programs with monoclonal antibodies: a CGRP (calcitonin gene-related peptide) agonist, aimed at migraines and other serious headaches, and the nerve growth factor inhibitor, tanezumab, to treat joint and low-back pain. Medicines engineered to treat specific pain conditions may alleviate some of the pressure on opioid use for permanent-pain inflictions that remain intractable to any other treatment. But safety standards will be especially high for any new pain drugs, and the business will be plowing new ground in this area as well.

The Company Within

In many ways, Lilly Bio-Medicines follows an autonomous business model, making it and each of the other business units resemble a company inside a company. And for everything but the general and administrative functions shared by all or most other business units in the corporation and its collaboration with the global manufacturing and quality organizations, the unit operates independently. It has responsibility for all R&D and commercial activities for products in its portfolio.

Above all, says Ricks, each business unit has the highest responsibility for maintaining a direct "line of sight" to its customers, from development to market. Introducing the concept of "eye on the customer" in 2009, John Lechleiter was preparing the company for a recovery of growth despite the difficult times ahead — when patent expirations for major products would tend to separate the company from its customers.

Some of those customers have grown much larger, and a little testy, during the same period. Big payers and PBMs (pharmacy benefit managers) have brought de facto customer consolidation and clout to the pharma industry at last, and Lilly Bio-Medicines tries to meet them on common ground. "We very much think of the major U.S. payers as customers," Ricks says. "That doesn't mean we do everything they want, of course. There's a tension there between capturing value for our shareholders and reward for the innovation we created, making sure the drugs that we invented to help patients actually get to the people who need them. The payers are the gateway to that goal, so we need to collaborate with them."

Ricks says good customer relations depend on finding the overlap between the unique challenges each large customer has and the solutions Lilly offers. "It is the art of the possible. Payers are under a lot of pressure, too, but my personal view and philosophy is we all want to help people who are sick, so let's start there and work together from that point."

Ricks cites the company's success in finding areas of common ground and "value points that both sides can live with" as helping it strike a couple of high-profile agreements with large insurers for "value-based pricing." Under the agreements, Lilly indexes discounts to the performance of the drugs according to specific measures. "Moving to that kind of thinking creates a lot of opportunities for everybody to sit on the same side of the table. If the drug works, they pay for it; if it doesn't, there's a big discount, and that tends to waylay a lot of concerns about drug pricing and value."

Valuable Traditions

To an outsider, it is easy to see Lilly throughout history as keeping its integrity and remaining durable while the world changed around it. Does it seem the same to an insider? Well, it does appear to come sincerely out of everyone's mouth, in spontaneous ways.

"We do see ourselves as kind of a steady, Midwestern-grounded company, and we want to stick to what we know how to do — discover or partner and then develop important new medicines," Ricks says. "There's always a place for specific acquisition of a technology or a product, and we've done a fair amount of that, but corporate-level acquisitions that really change the nature of your company are so distracting in an innovative business where time and speed matter so much. We avoid those distractions, because innovation is the spring of our success."

If the company's Midwest center presents a challenge, it is the risk of isolation from the external forces and larger pharma/biopharma communities on opposite coasts. Yet, as Ricks maintains, the location may also encourage long-term thinking, a focus on execution, and coherent action. "And for a company that's big, it keeps it small, too. Everyone who's been here knows each other. You can move more quickly; it's easier to communicate and get things aligned." One cogent example of Ricks' argument is his working ties with the heads of manufacturing and quality featured elsewhere in this feature: "Maria Crowe and Fionnuala Walsh are integral partners for me in everything from early development of particularly complex biologics to managing the commercial products. With all of the patent expirations, we must reduce the asset base of manufacturing technologies that are expiring while investing in the new asset base of technologies, years before the new products launch."

See "Making Quality," with Crowe and Walsh, to learn more about Lilly's global manufacturing and quality organizations, which are also critically important to the diabetes business unit featured in the next section. ▸

STILL INSULIN
And Beyond

Like David Ricks and the other executives in this extended feature, Enrique Conterno has spent his career at Lilly, in his case, 24 years. He has had a multifunctional experience as he gained increasing responsibility at the company, with assignments in sales, finance, marketing, and business development. That included some time as head of sales and marketing in his home country, Peru, and Brazil, and as general manager of the company in Mexico. Also like Ricks, Conterno served for a time as president of Lilly USA. He became president of Lilly Diabetes in 2009.

"What's exciting about this role is the ability to look at diabetes and lead the business from all types of perspectives, to integrate very different parts of the organization, from development to manufacturing to the worldwide globalization of our medicines," Conterno says. "Before we created the business units, we were organized in functional silos, and all of our operations only came together at the level of the CEO."

He says the company saw an opportunity to realign its "value chain" of operations around therapeutic categories, and he echoes Ricks in using the phrase spread by Lechleiter around the company: "We now have a better line of sight to our customers all across the organization. We are also able to operate today with much more agility in our decision making and execution, and that basic strategy is paying off for us."

Functional Intersection

Conterno's Diabetes unit has another thing in common with Bio-Medicines — the critical roles of manufacturing technology, infrastructure, and organization in its business growth. A joint governance committee is a built-in mechanism that regularly brings him together with Maria Crowe, head of global manufacturing, and Fionnuala Walsh, head of global quality, to share planning and decision making. Such collaboration has led to important insights about creating operational efficiencies, he says.

"Rather than thinking about our different products on a stand-alone basis, we needed to think about our insulin and technology platforms. Together, we developed ways of making our plants more flexible, and today our plants have the ability to manufacture any one of our insulin products. We also rethought how we make our insulin, and we decreased the number of steps in the process, consistent with our quest to decrease costs and become more competitive in the long term."

Conterno emphasizes the need for both affordability and quality in the diabetes market, especially with the products needed for daily use of insulin. "An injector pen, whether disposable or reusable, has to work 100 percent of the time in the right way — meaning with every single dose it is important that it's delivered with the appropriate accuracy." As an independent business unit, he says, Lilly Diabetes can better judge its own performance in those areas against the competition, and it keeps another sharp eye on its competitors.

The improvements to Lilly's insulin production also led to a large change in plans. As recently as 2014, the company intended to build a new, much larger plant to replace its existing facility in Indianapolis. But Conterno says the huge boost in efficiency brought on by truncating the insulin-making process and reworking plants to produce all insulin products made building any new plant unnecessary. Instead, the company did extensive remodeling within its existing footprint of insulin manufacturing facilities, doubling its output and lowering costs in the bargain.

"The new efficiency has allowed us to think a little more long term," he says. "Now we have a capacity that can support the growing business."

Close collaboration with manufac-

ENRIQUE CONTERNO
President of Lilly Diabetes

turing and quality has also aided the development side, where new products require careful formulation and process development, and later-stage candidates need production flexibility and support such as monitoring, dose-adjustments, and combination-therapy engineering. Based on research indicating synergistic benefits of some agents used together, several of the diabetes products in the pipeline are drug combinations.

Community Service

Lilly Diabetes has hosted a "diabetes bloggers summit" at the remodeled insulin plant in Indianapolis — just one of the ways it is taking pains to gauge patients' gut feelings about the company's leadership and responsiveness in the patient community. Conterno explains how patients came to play such a center-stage role for his business:

"From a historical perspective, our industry, in particular Lilly, has always been extremely focused on dealing with healthcare professionals, but in reality, patients now have access to much more information than they did even five years ago. So it has become critical for us to ensure we are significantly engaged with the diabetes community at large. To that end, we believe we have to engage both with the people who are huge advocates for us and also with our critics. By engaging in that way, sometimes we achieve a better understanding on both sides."

Going beyond the usual market research with patients for product development, the diabetes unit has ventured deeper into social media to reach its patient base. At the same time, adds Conterno, the business must be careful not to transgress legal barriers to anything that might be judged as marketing or sales of prescription drugs.

"People are willing to engage, and they're really thirsty for more diabetes information, as long as the information is relevant to their needs, so we're constantly exploring different avenues in which to engage," he says.

Occasionally, as the web would have it, social media spill over into mass media. Conterno describes a serendipitous foray into the public realm — in a Super Bowl commercial. In the spot, NASCAR Xfinity driver Ryan Reed, a role model for Type 1 diabetes patients, re-enacts his previous win at Daytona this year to say, "You can do it all!," then showcases a Lilly Diabetes information program for patients.

To patients, physicians, payers, and customers in general, Conterno says his business unit has listened carefully and responded with something more than selling. Many kinds of companies employ the metaphor of offering solutions, but when a business serves a patient base with chronic, daily needs for life-giving drugs and delivery devices, the solutions are real and material, not rhetorical. In Conterno's case, you could argue it also gives him some bragging rights:

"We have the broadest portfolio of solutions in the industry. Now we're launching new products, and our recently launched products are leading the market in the United States, Europe, and Japan. We are actually gaining market share with every Lilly product in every diabetes category. That's quite unique given we have a mix of mature and newer products, but I attribute that to our innovation in creating solutions with our entire portfolio."

Perhaps the solutions Lilly Diabetes offers, coupled with its competitive "affordability" strategy, will carry through the external pressure waves now hitting the entire industry, often in contradictory ways. "The public has questions about whether medicines are affordable enough, particularly in the U.S. market. But when I speak with analysts, typically their No. 1 concern is whether prices are deteriorating due to competition."

With Humalog, the top diabetes product in the United States, the price has been essentially flat during the past five years, according to Conterno. On a net basis, list prices have not increased because payer rebates are significantly more consolidated today, a trend that will lead to financial challenges if it continues. Yet he remains sanguine. "We see significant pressures ahead, but they're just part of the business, and why it's so important that we look at ways to be more efficient on the marketing side or the manufacturing side, so we can make our medicines as affordable as possible."

To see the same theme carried through and put into action on the manufacturing and quality sides, continue reading with "Making Quality." ▸

By W. Koberstein

MAKING *Quality*

The following women lead two of the most critical organizations for Lilly's growth and product development.

Maria Crowe has been with Lilly for nearly a lifetime. After graduating from Purdue in 1982 with a degree from the business school in industrial management and a computer science minor, she joined Lilly first in the IT area but then moved to manufacturing a few years later. She had two long international assignments, one in Puerto Rico and one in Ireland, where many of the company's leading medicines were produced for the past 30 years. Thereafter, she had a variety of roles supporting multiple manufacturing plants, and in 2012, she took on the lead responsibility for global pharma manufacturing, which includes all of Lilly's own manufacturing sites, as well as its contract manufacturing organizations.

Fionnuala Walsh joined Lilly in 1988, after earning her bachelor's and doctoral degrees in chemistry from University College in Dublin, Ireland. She began at the manufacturing site in Kinsale, Ireland, working in technical services, project outsourcing, new-product introductions, and laboratory analytics. During the following years, she rose through positions of increasing responsibility for managing quality and manufacturing science and technology, becoming global quality leader in 2002, vice president for global quality operations in 2005, and head of global quality in 2007. Lilly Global Quality is a stand-alone organization with about 2,000 employees worldwide, monitoring, auditing, and ensuring adherence to regulatory and company quality standards all along the supply chain, including supply chain security and prevention of drug shortages. Its Lilly Quality System defines "quality requirements for processes throughout the product development cycle."

What Essential Elements Of Lilly's History Do You Believe Are Especially Relevant Today?

CROWE: Our manufacturing heritage in the company really goes all the way back to the very beginning, because Colonel Lilly instilled the principles of science and quality from the start, and the heritage has continued through the entire history of the company. In manufacturing, we make medicines, with safety first and quality always, and the patients should never have to question whether what they're taking is right, because it's our responsibility to ensure that it meets the highest quality standards in every case. As an example, insulin was discovered in Canada by Banting and Best, but they couldn't figure out how to make insulin at commercial scale, and that's where Lilly came in. So we helped them to develop a process that made high-quality insulin usable for millions of people.

WALSH: Our products can be sold in any market in the world based on quality. There was an old saying in a Lilly advertising campaign back in 1929, "If it bears the red lilly, it's right." I still like to think of it in that way. It means our product was designed right, it was made right, and it was sold in the right way. We put a lot of effort into the science of the products, and we also have a single quality system for the whole company. We are intentional about the standards we expect from our facilities, processes, analytical methods, educational programs, and everything else that affects product quality.

Big Pharma companies in general are not known for their forward-thinking, up-to-date manufacturing methods and quality, but Crowe says Lilly, in keeping with its traditions, develops and uses highly advanced technologies not only for its quality advantages but also for efficient coordination of its integrated resources.

What Would Be Some Good Examples Of Your Advanced Technologies?

CROWE: If you came into our manufacturing sites, you would not see many people touching the product, because most of it is operated via electronic systems that are managed from a computer screen. As an example, our monoclonal antibody biologics is very sophisticated, and the equipment is set up to be extremely clean. Many visitors expect to see an old-fashioned scene with people along our production line, but our facilities look very different from that.

We also have a sophisticated set of IT solutions that all of our manufacturing plants share, so we can easily look at our data, aggregated or disaggregated, anywhere around the world. We benchmarked our IT a few years ago with an external consulting firm, which indicated our set of IT solutions was probably more sophisticated than any other company's. Many companies have multiple versions of SAP running in different parts of their business, whereas we have one global solution, as an example.

WALSH: Our IT is unique, probably also because we've had the advantage that we haven't merged with another company. In the major pharmaceutical firms that have merged many times, each acquired company brings its own culture and its own IT systems with it, and trying to integrate the different systems has been a considerable challenge. Being free of that challenge allows us to focus on innovation and come forth with a wonderful pipeline. We are now probably fighting above our weight in innovative products. If you're spending all your energy trying to integrate new organizations, the focus gets diluted.

So Manufacturing And Related Systems Such As Information Technology Play A Key Role In Innovation?

CROWE: Yes. Manufacturing has played a key role in the scientific breakthroughs Lilly has made throughout history. But also, you can't sell anything if you can't supply it, so it is key that we have product available when we're ready to sell it. That requires working with our development organization to collectively bring new products to patients faster — to reduce the cycle time from development to manufacturing to launch by creating a seamless approach among various related areas inside Lilly. That is game changing, as opposed to each component of the company looking at it from an independent standpoint.

Manufacturing and Quality play strong strategic roles in the company; Crowe and Walsh sit on the executive committee, involving them with R&D output, business strategies, and launch plans — and allowing them to coordinate with colleagues on how their organizations can support the overall mission of the company.

WALSH: When you are taking a product from development to manufacturing, you are really locking in up to 80 or 90 percent of your innovation at that point. In building a house, you can change the plumbing if the house is at the framing stage, but if it is all built and finished, changing the plumbing is a much more difficult and comprehensive affair. The intimate knowledge of a product that manufacturing and development share is essential to ensure the most efficient and effective use of our facilities, and that is truly game changing.

What Are Some Of The Ways You Are Strengthening Manufacturing And Quality In The Global Organization?

CROWE: We definitely are a global organization. In fact, more of our manufacturing sites and more of our manufacturing employees are outside of the United States than inside. However, we do have one strategic framework in which we operate. Our Operational Excellence Program defines the structure of each manufacturing site and the main ways we govern our operations for safety and quality. We also have a common set of metrics, monitored on a regular basis from each of our internal manufacturing sites and external contract manufacturers. It is a process replicated around the world that allows us to bring products to market faster, and to ensure we can supply all of the products as needed for the market. As we move people to different jobs and into different roles around the world, the system allows us to operate from a common framework.

WALSH: In some companies, quality is considered to be compliance alone, and compliance is extremely important to a very complex regulatory environment — brought about, I might add, by bad science or bad performance in the industry. But compliance is only part of the story at Lilly. The real story here is about the people who put real science and work into how they make the medicines. It's not checking quality at the end of the line, although that is required — the most important part of quality is built into our everyday work and culture.

MARIA CROWE
President of Lilly
Manufacturing Operations

FIONNUALA WALSH
Senior VP of Global Quality

How 2015's Patent Law Trends Will Affect Life Sciences Companies

GREG DELASSUS

Greg DeLassus is a patent attorney with Harness Dickey, securing patent protection for biotech and pharmaceutical innovators.

Although 2015 did not produce any explosive new developments in patent law from the Supreme Court (like the Myriad gene patenting case in 2013) or from Congress (like the America Invents Act in 2012, also known as the AIA), the past year did witness the emergence of two important trends in life sciences patent law. These trends concern: (1) increasingly difficult standards for life sciences inventions to be considered eligible subject matter for patenting; and (2) low cost, expedited procedures to contest patent validity after grant.

SUBJECT MATTER ELIGIBILITY AND THE MAYO REVOLUTION

To understand the significance of the changes that emerged in 2015, a little background knowledge is needed. U.S. courts and the Patent Office have long considered that you cannot patent a diagnostic or therapeutic method that takes place entirely in a physician's head (e.g., "look at the patient's dilated pupils and decide that the patient has a concussion"). However, so long as the method involved some physical steps (e.g., "measure blood lead concentration and diagnose lead poisoning") it was eligible for a patent.

This changed in 2012 when the Supreme Court announced a new rule for analyzing the subject matter eligibility of a medical treatment process at issue in Mayo Clinic v. Prometheus Labs. The Mayo rule holds that if the method's physical steps involve routine or conventional techniques, they do not count in assessing patent eligibility. In other words, if your invention involves, for example, measuring expression of a certain gene and then prescribing a particular medicine, the "measuring" part does not count toward assessing eligibility because gene expression can be measured by conventional techniques like PCR (polymerase chain reaction).

The Mayo rule was such a startling break with past practice that the court of appeals for the Federal Circuit (i.e., the court that hears almost all appeals involving patents, also known as the CAFC) was initially hesitant to apply this new rule too vigorously. However, the Supreme Court reiterated Mayo in 2013 (ACLU v. Myriad Genetics) and again in 2014 (Alice Corp. v. CLS Bank). The CAFC "got the message," so to speak, in 2015 and began applying Mayo more aggressively. The CAFC's more recent approach is to start an analysis of patent eligibility by asking "does this invention involve a natural product, law of nature, or abstract idea?" If so, then you mentally bracket that element and look at the rest of the patent claim, ignoring any parts that concern routine or conventional technologies (e.g., PCR, affinity purification) to decide whether the claim as a whole still adds up to something that fits into a category of a patentable invention. Because most life sciences inventions involve either a natural product or a law of nature at some point, this new approach to analyzing patent eligibility invalidates many life sciences patent claims.

THE ARIOSA EXPANSION

In Ariosa v. Sequenom, the CAFC applied a very aggressive version of the Mayo rule to invalidate a patent covering an invention that can diagnose fetal abnormalities without amniocentesis by detecting fetal DNA in the mother's blood. All of the judges who heard the case agreed that the invention was innovative and brilliant, but because the invention involved fetal DNA (which is a natural product) and PCR (which is a conventional technique), the CAFC held that the invention claimed was not patent eligible.

The Ariosa case was so controversial — because the technology involved was so clearly useful and innovative — that the CAFC was asked to take a second look at the case (so called "en banc" rehearing). Although the judges ended up reaffirming their original decision, they did suggest other ways that the patent could have been written that might have changed the outcome. In particular, the order denying en banc reversal indicated that if the patents had been limited to just the aspects of the invention that had been tested and proven workable (i.e., if the patents did not also cover methods that were very likely to work in view of the data, but which had not yet been tested), they might still have been valid.

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EXECUTIVE ACTION ITEM

Companies whose technologies involve isolated natural biomolecules or correlations between biomarkers and a disease should have an attorney review any patents that were issued before 2015 to make sure they include the sort of narrow claims that have been suggested to still be eligible in view of Ariosa. If such narrow claims are not already in the patent, it may still be possible to seek a reissue examination to add such claims.

POST-PATENT GRANT OPPOSITION PROCEEDINGS

The 2012 AIA created a low-cost alternative to litigation to deal with situations where one party thinks that another party's patent claims are invalid. Instead of suing in court to invalidate the patent, the challenger can file a brief explanation of the challenged patent's perceived defect with the Patent & Trademark Office (PTO). If the PTO agrees, an administrative trial is instituted and directed only to patent validity, not infringement. The trial is supposed to run for no more than 18 months — sometimes no more than one year. This creates a very efficient — and much less expensive — way for a company to clear away a blocking patent that it believes to be invalid.

Because these proceedings only came into effect late in 2012, it was not until 2014 that we started to get an appreciable number of decisions from the PTO about what sort of patents are liable to be invalidated. Only in 2015 did we start to get decisions from the CAFC indicating how the courts will review PTO decisions on appeal. Two trends can be broadly discerned from the decisions we have so far: (1) the PTO has been generally less willing to invalidate biotech and pharmaceutical patents than patents directed to software and business methods; and (2) the CAFC is very unlikely to reverse the PTO's decision.

THE EFFECT ON PHARMA AND BIOTECH

The relatively low cost of these proceedings (compared to litigation in court) has made them very attractive to two sorts of entities with particular relevance to the biotech and pharmaceutical sectors. The first of these is generic and biosimilar drug manufacturers. Because a generic or biosimilar drug cannot enter the U.S. market until all patents covering the FDA approved product are expired, generics can often accelerate their entry into the U.S. market by months or even years by attacking the latest expiring patents in the PTO.

A second group of life sciences-related entities have also emerged as a result of these PTO proceedings: hedge funds that call themselves patients' rights groups. Although Kyle Bass' "Coalition for Affordable Drugs" is probably the most famous of these, it is not the only hedge fund whose business model is built around attacking late-expiring patents covering brand-name drugs and trading stocks of players in the relevant markets.

Both of these groups — the generic manufacturers and the hedge funds — have the same interest: shortening the term of protection on life sciences' inventions. Most patents covering life sciences technologies have more than one claim, where some of the claims are broader, and others are narrower. The PTO has shown itself more willing to invalidate the broad claims than the narrow claims. However, the FDA will not usually give a generic manufacturer approval to enter the market so long as there is even one claim still covering the product on the market. Therefore, it is very important to have at least one claim — no matter how narrow — that can survive a validity challenge.

EXECUTIVE ACTION ITEM

In view of the new AIA proceedings, every life sciences company should have a patent attorney review the company's patent portfolio (including pending applications) to make sure that the requisite narrow claims are present. Frequently, early patents will have been issued years ago, before all of the details of the market product were entirely settled. If you have a better picture now of the market product than you had back when the patent(s) were issued, consider requesting a reissue examination to add new claims to the patent that more narrowly cover the market product. Such narrow claims could make all the difference in a validity contest.

THE BIG PICTURE

Both of the trends discussed above (tighter standards for patent eligibility and easier review of potentially invalid patents) are good for companies that need freedom to operate in the face of patent claims belonging to competitors. Both trends are bad for companies that need to secure and enforce patent claims for their own intellectual property. In other words, 2015 brought good news and bad news for life sciences innovators.

Life sciences companies need to pursue future patents with these two trends in mind. They also need to review existing patents to determine whether claims that once might have been sufficient are possibly less secure in view of these trends of 2015. If the 2015 trends have introduced weaknesses into your patent portfolio, it is probably not too late to fix these problems, but only if you take a proactive view to protecting your company's intellectual property. L

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Singapore's Evolution To A Top Phase 1 Trial Destination

CHRISTOPHE TOURNERIE AND YEW LAY HWA

Singapore can be considered as the R&D spearhead in Asia with cutting-edge technology, top clinicians, a solid and advanced infrastructure which rivals the West, as well as drive, commitment, and investment by its government to become one of the preferred clinical research destinations worldwide. The country plays a substantial role in conducting Phase 1 studies in the Asia-Pacific region. Many pharmaceutical and biotech companies are now choosing to bring their innovative early-phase trials to Singapore over the more conventional options of the United States or Europe. This is largely due to the success stories during the last five years.

A MULTI-ETHNIC CLINICAL RESEARCH ENVIRONMENT

Singapore can provide an inimitable clinical research environment. The access to multi-ethnic populations is one of the unique advantages it can offer; the country's population is composed of 74.2 percent Chinese, 13.3 percent Malays, 9.2 percent Indian and Eurasians, and other groups make up 3.3 percent of inhabitants. As such, it allows R&D companies to conduct multi-ethnic comparisons to establish the effects on different races, all in a single location — a location which the FDA and EMA (European Medicines Agency) will consider much more favorably than trials conducted in each of the countries of origin for those population groups. The drive by Singapore's government to be a first-class clinical research destination has meant time has been spent ensuring the Health Sciences Authority of Singapore (HSA), the local regulatory body, has streamlined processes in place, thus allowing for faster approval timelines than not only the majority of other countries in the region but also globally. There is also a confidence in clinical trial data coming from Singapore, with leading GCP-trained investigators and sites, as well as an assurance that international quality standards are applied. The ability to rapidly recruit for these early-phase studies also ensures shorter trial timelines and, therefore, less overall expenditure.

Other developed countries in the region that have the infrastructure to conduct reliable Phase 1 studies, such as Korea, Taiwan, and Hong Kong, are less experienced in international clinical trials. Additionally for Phase 1 studies, more data needs to be provided, and timelines are longer than conducting later phase trials.

Singapore is central to the region and the hub of the life sciences industry, acting as a springboard to carry out further development across the rest of Asia as a candidate moves through the later phases. Conducting a Phase 1 study in Singapore can help an R&D company learn about the intricacies of performing development activities in Asia. In addition, choosing Singapore for these studies exposes a company to a new set of investors from a wealthy country.

WHERE TO CONDUCT PHASE 1 STUDIES IN SINGAPORE

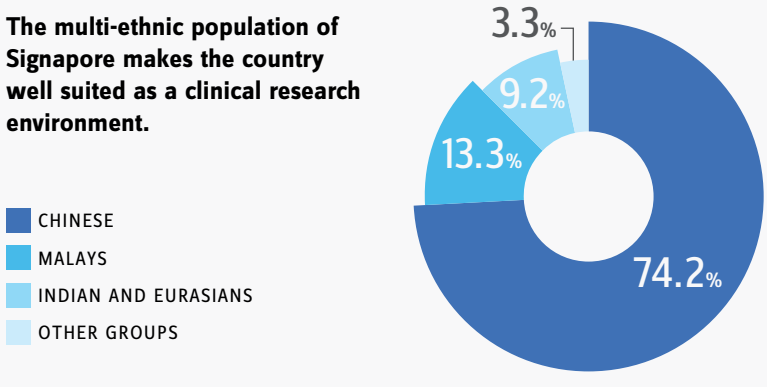
There are three public independent units in Singapore where Phase 1 studies can be conducted, not including those for oncology studies:

1. Changi General Hospital
2. Sing Health Investigational Medical Unit
3. National University Clinical Trials Unit

All of these units are very active and operate as extensions of the hospitals themselves, providing on-site support to investigators, as well as safety, security, and reassurance for study volunteers. In Singapore all units operate to the same stringent standards and efficiencies, with leading investigators at the helm and continued substantial investment from the government, for advanced infrastructure to support clinical trials. All of these factors make it easy to implement an early phase trial in the country.

The Clinical Trials and Research Unit (CTRU) at Changi General Hospital is run by highly experienced site personnel and provides the high level of medical sophistication essential for first-in-human

The multi-ethnic population of Signapore makes the country well suited as a clinical research environment.



studies. Since inception, the unit has conducted 39 industry-led Phase 1 studies. This unit specializes in pharmacokinetics, pharmacokinetics-pharmacodynamics, and pharmacogenetics studies, as well as studies on ethnic sensitivity testing, thorough QTc (corrected QT) and the effects of age and gender, drug-drug, and drug-food interactions.

CONSIDERATIONS FOR CONDUCTING PHASE 1 TRIALS IN SINGAPORE

- In Singapore, for first-in-human studies, the drug does not need to be approved in other countries before the study can be performed.
- For guidance on nonclinical and clinical requirements, Health Sciences Authority of Singapore (HSA) refers to applicable International Conference on Harmonization (ICH) guidelines and relevant guidelines issued by the major agencies such as the FDA and EMA.
- An export license is not required from HSA for shipping of biological samples overseas for testing.
- In general the documentation requirement to support FIH (first-in-human) applications is not significantly different to that for later phase studies.
- If the investigational product is of a novel therapeutic class or mechanism of action, a presubmission meeting between the sponsor and regulatory authority can be arranged.
- Clinical trials materials imported into Singapore are exempted from goods and service tax of 7 percent.
- No fees are required for regulatory review or issue of a clinical trial certificate.
- English is the official language in Singapore. As English documents are sufficient for the initial submission dossier, a fast start-up time of four to six weeks is typical.
- Well-established, centralized drug depots are located in Singapore. Sponsors can utilize either direct shipment of IPs and trial materials from overseas to sites directly or have the materials stored at these depots for faster replenishment of materials at sites. L

Dr. Christophe Tournerie is the founder and CEO of ClinActis Pte Ltd., a CRO that specializes in conducting clinical research in Asia Pacific.

Yew Lay Hwa is the assistant director of clinical trials & research unit at Changi General Hospital. She has extensive experience with clinical trial site management.

Why Now Is The Time For Pharma To Expand Into Africa

CATHY YARBROUGH Contributing Writer @sciencematter

Africa's status as one of the fastest-growing economic regions in the world has transformed the continent from a focus of corporate social responsibility to a potential major profit center for the global pharmaceutical industry. In a world of slowing and stagnating markets, Africa represents the last geographic frontier where genuinely high growth is still achievable, said Tania Holt, principal in McKinsey and Company's Johannesburg, South Africa, office.

As a result, industry leaders such as GSK, Novartis, Sanofi, and AstraZeneca have been expanding their commercial footprints into Kenya, Nigeria, and other sub-Saharan African countries outside of South Africa. Today almost every major multinational pharmaceutical company is represented in one or more of Africa's 54 nations, said Holt, co-author of the 2015 McKinsey report, *Africa: A Continent of Opportunity for Pharma and Patients.*

GSK is one of the Big Pharma companies in Africa for the long haul. In 2014, the company announced that over the next five years it would spend $216 million to expand the continent's healthcare training, science education, and R&D infrastructure. GSK also announced that the cost of its patented drugs in Africa would not exceed 25 percent of the price charged for the medications in the U.S. GSK announced in March 2016 that it no longer would seek patent protection for its drugs in UN-designated least-developed countries, many of which are located in Africa. This new policy will allow generic companies to manufacture generic versions of GSK's patented drugs in those countries.

These initiatives are a long-term strategic investment to drive the company's business growth on the continent, said Allan Pamba, M.D., GSK's VP of pharmaceuticals for East Africa and VP for government affairs for Africa. "GSK is willing to make a small return now because we have a long-term view of the market potential of Africa," said Pamba, who was born and educated in Kenya.

Undergirding the pharmaceutical industry's long-term view of Africa as a potential economic engine of growth are the following data points from the McKinsey report:

- Africa's pharmaceutical industry grew from $4.7 billion in 2003 to $20.8 billion in 2013. By 2020, the continent's market value should total $40 to $65 billion.
- Also by 2020, the continent's GDP is expected to reach $3.3 trillion. In 2013, the GDP was 2.4 billion. (Pamba pointed out that with rapid economic growth, Africa has become much more politically stable.)
- Consumer spending, which totaled $1.8 trillion in 2013, is expected to reach $2.4 trillion by 2020.
- Healthcare spending rose from $28.4 billion in 2000 to $117 billion in 2012. During the same 12-year period, per capita expenditure almost tripled from $41 to $112.

- During the five-year period ending in 2020, strong growth can be expected in Africa in medical devices as well as prescription, generic, and OTC drugs.

In recent months, concerns about Africa's growth have emerged as a result of the recent plunge in oil prices in the continent's oil-producing countries and the economic downturn in China, a major business investor on the continent. "The fundamentals are still very strong," Pamba said. "As an emerging market, Africa is 15 to 20 years behind India's economic cycle. Now is the opportunity to grow and invest in Africa."

"Demographics continue to paint a positive picture long-term," said Holt. "Africa's population is young and growing at a rate faster than any other continent." About 60 percent of Africa's current population is below the age of 35.

> *"As an emerging market, Africa is 15 to 20 years behind India's economic cycle. Now is the opportunity to grow and invest in Africa."*
>
> **ALLAN PAMBA, M.D.**
> VP of pharmaceuticals for East Africa and VP for government affairs for Africa, GSK

"AFRICA RISING"

The continent's rapidly expanding young population is one of several factors responsible for Africa's improved economic development, often referred to as "Africa Rising." Another factor is the continent's rapidly expanding middle class. By 2025, the annual income of 70 percent of African households will be higher than $5,000, which in the developing world is the entry point for an emerging middle-class lifestyle with sufficient discretionary income to spend on health, according to the McKinsey report.

Africa's growing middle class also has more discretionary income to spend on high-calorie, high-fat food and cigarettes. As a result, an epidemic of hypertension, diabetes, and other noncommunicable diseases (NCDs) is "brewing in Africa even as we begin to turn the corner on communicable diseases such as HIV/AIDS and malaria," Pamba said. According to the World Bank, NCDs were responsible for 28 percent of deaths in sub-Saharan Africa in 2008. By 2030, deaths from NCDs are expected to increase to 46 percent.

"There is a narrowing window of opportunity to stave off or mitigate the NCDs epidemic by strong investments in prevention," said Pamba. "Failing that, the increase of NCDs in the African population puts Africa in the same market opportunity as developed countries — and relevant for the many multinational pharmaceutical companies whose portfolios include drugs for heart disease, high blood pressure, diabetes, and cancer."

Also contributing to Africa's rise is the urbanization of the continent. Today an estimated 37 percent of the African population lives in 30 key cities. By 2030, about 50 percent of Africa's population will be city dwellers, according to the McKinsey report. "By focusing its efforts on the pockets of growth in each target country, a company can obtain high commercial impact," Holt said. However, because the barriers to access often differ in cities and rural areas, companies must develop fundamentally different business models for each population.

Most pharmaceutical companies are focusing their commercial efforts on the 10 African countries responsible for more than two-thirds of the continent's GDP and cumulative growth over the past decade. "Companies have become very granular in their strategies," said Holt. "Before they make an investment, they want to know whether they're in the right country, have the right drug portfolio for the country's healthcare problems, have the right supply hub, and are interacting with local governments at the appropriate level."

REIMBURSEMENT IS TOP BUSINESS CHALLENGE

Kenya is one of the 10 African countries that pharma is focusing on. It is considered by many a gateway to East Africa because the country's logistically well-connected capital, Nairobi, provides access to surrounding East African countries. In West Africa, the anchor points typically are Lagos in Nigeria as well as either Dakar in Senegal or Abidjan in the Ivory Coast. Nigeria, the West African nation in which most companies have set up operations, is the most populous country and has the largest economy on the continent. "Because of demographic and economic factors, Nigeria is often referred to as the 'next South Africa,' from a healthcare potential perspective," Holt said. GSK's robust commercial operation in Nigeria includes a large manufacturing plant. Kenya and South Africa are the sites of GSK's other manufacturing facilities on the continent.

In Kenya, Nigeria, and the Ivory Coast, reimbursement is one of the top business challenges for drug companies. Health insurance is available to only 20 percent of the South African population and just 3 to 6 percent of people living outside South Africa. Therefore, because most Africans must pay out-of-pocket for their medications, pharmaceutical companies must take a different approach to pricing and reimbursement on the continent than they do in developed countries.

Since 2014, GSK's approach to pricing and reimbursements has been capping the price of its patented medicines. Even though GSK's drugs and vaccines are sold at a steep discount in Africa, the British company's commercial operations are profitable, said Pamba. "In addition, we are increasingly launching our new drugs in Africa in the same year when we launch in the U.S and Europe, keeping Africa in step with the leading global economies," he said.

GSK evaluates Pamba's performance

in part by the quantity of the British drug company's products that he and his team distribute in East Africa. "We have adopted a high-volume, low-margin business model, because our goal is to reach as many people as possible," said Pamba, whose GSK offices are based in Kenya.

In addition to pricing, the lack of healthcare workers is a major challenge for pharmaceutical companies in Africa. "This means that the number of patients who come in contact with the healthcare system and obtain a correct diagnosis and treatment is very limited relative to what it could be," Holt said.

Several drug companies have launched training programs to boost the number of healthcare workers in Africa. In 2014, GSK announced its Least Developed Countries initiative, in which 20 percent of the company's profits from the African market is used to fund the training of additional healthcare personnel on the continent. Pamba said that GSK regards the program as a long-term strategic investment to drive the company's business growth in Africa. Thus far, 30,000 healthcare professionals in low- and middle-income countries in sub-Saharan Africa have completed GSK-sponsored training, which is conducted by two NGOs, Save the Children and the African Medical and Research Foundation, as part of the UN's One Million Community Health Workers campaign.

Inadequate public awareness of NCDs is another challenge for pharmaceutical companies in Africa. To obtain an accurate diagnosis and the best treatment, patients must know that they need to seek healthcare. "People must be aware that diabetes and high blood pressure exist, and that there are effective treatments for these disorders," she said.

ONE SIZE DOES NOT FIT ALL

The McKinsey report recommends that drug companies collaborate with health ministries and NGOs to develop and conduct public awareness campaigns, health screenings, and treatment in core therapeutic areas. According to the report, "Such relationships give companies opportunities to work on important issues such as counterfeiting and intellectual property rights, while also allowing them to develop expertise in markets and health systems and play an active part in improving public health in Africa."

Another challenge for pharmaceutical companies is the distinct nature of each of the continent's 54 countries. Africa is not one market, but many markets, each with its own legislative code, macroeconomic landscape, and political complexities. In addition, the regulatory environments vary from country to country in Africa. "A one-size-fits-all approach does not work in Africa," said Holt. "The pharmaceutical companies that appear to be the most successful have the ability to get a real grasp of the local understanding and granularity."

Hiring local talent is one way to achieve local understanding. "Our experience indicates that successful companies focus on building strong local teams, forging local partnerships, and addressing supply and distribution challenges," said Holt.

However, talent is still scarce in Africa. By 2020, just 8 percent of Africa's population is expected to earn tertiary degrees. Drug companies must compete for talent staff not only with each other but also with oil and gas, banking, and telecommunications companies. "So like any other industry in Africa, the pharmaceutical industry must play an active role in developing the next generation of leaders," said Holt. The McKinsey report recommends that companies consider building capabilities in-house and growing their own leaders. (McKinsey takes this approach in Kenya where the company trains promising young Kenyan professionals in critical thinking and quantitative analysis, as well as people skills such as cooperation and consensus-building.)

To help nurture Africa's scientific talent, GSK is establishing academic programs in the pharmaceutical sciences, public health, engineering, and logistics at several of the continent's major universities. GSK also has established an Open Lab for research and training on the prevention, diagnosis, and treatment of NCDs. The Open Lab is currently based at the company's R&D facilities in Stevenage, U.K. "A particular focus of the Open Lab is to support local African physicians in their studies to answer burning research questions such as why is there a high incidence of treatment-resistant hypertension in African populations, and why does breast cancer occur earlier in African women compared to their Western counterparts," said Pamba.

If the Open Lab existed when he was a young physician, perhaps Pamba would have applied and received a research grant to study HIV/AIDS, malaria, and the other infectious diseases that afflicted his patients in Kenya. When he was growing up, Pamba, like many children in Kenya, suffered from malaria. He was one of the lucky ones — he survived. When he was a medical student in Kenya, Pamba said that he never expected that the economy of his home country — and the continent — would become one of the fastest growing in the world. "Today when I travel the continent, I see a lot of happy faces, I see young Africans who are successful entrepreneurs, I see progressive governments, and I see hope," he said. "It is the dawn of a new era. My generation must carry forward responsibly, leaving no one behind." L

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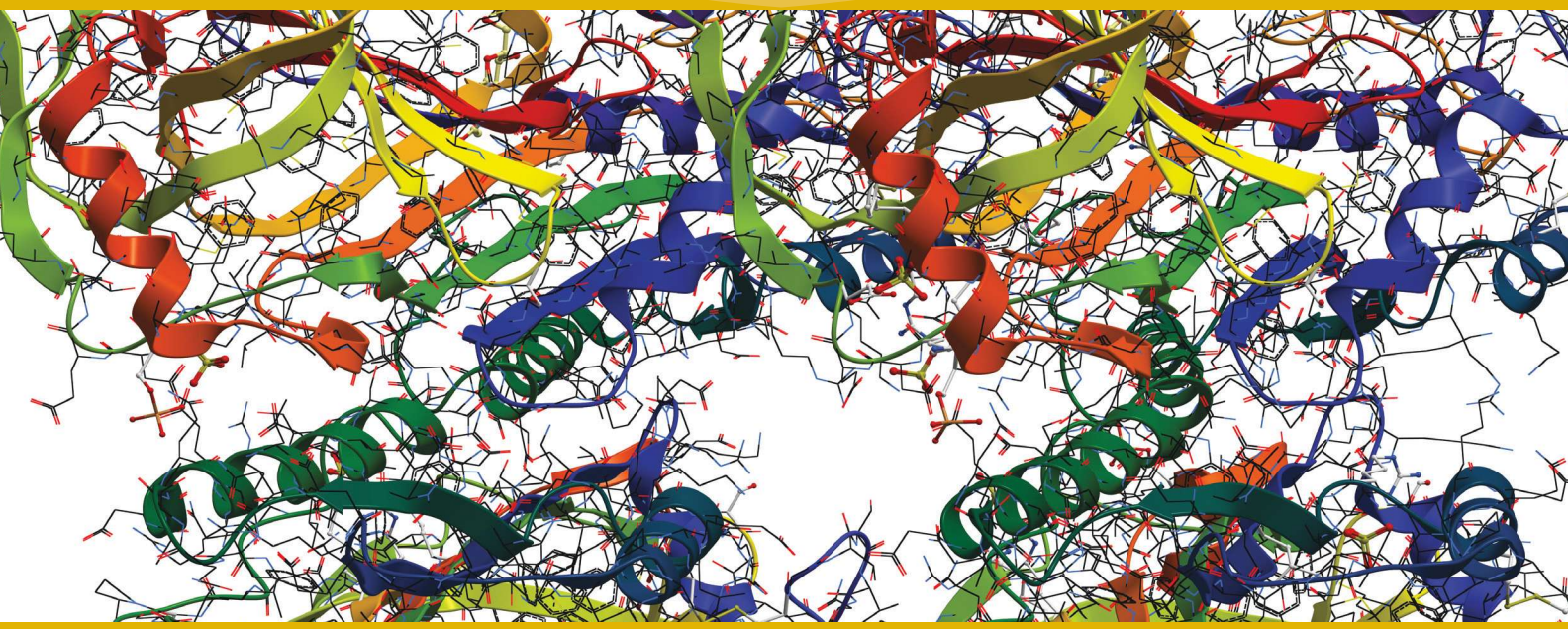

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#2016Bio

An Entrepreneurial Approach To Funding Drug Development

DAN SCHELL Editorial Director

The tech world is filled with stories of companies that grew from modest beginnings with minimal capital: Steve Wozniak and Steve Jobs tinkering in Jobs' garage; Michael Dell scraping together $1,000 to buy parts and build personal computers in his dorm room at the University of Texas.

The biotech world also boasts inspirational tales of success, but few with such humble beginnings. One reason for the disparity is that tech startups can get by with minimal investment in computers and space to house them, but biotechs typically need lots of equipment, lab space, and chemicals. In addition, tech startups don't have the regulatory requirements that biopharma startups do (e.g., the strict U.S. FDA rules for manufacturing drugs and for undertaking the safety studies necessary to start clinical trials).

Nonetheless, entrepreneurs set on turning new compounds into meaningful drugs are finding innovative funding solutions that give them a shot at becoming the next great biotech success story. One such pathway to growth relies on a combination of grants, partnerships with leading academic institutions, and small amounts of equity.

A case in point is Oncoceutics, now a clinical-stage oncology company that recently completed a Phase 1 and has multiple Phase 2 trials ongoing for ONC201, a novel oral cancer drug that works differently from other cancer drugs on the market. Founded by a renowned oncology researcher, Wafik El-Deiry, and two veteran life science industry executives and investors, Wolfgang Oster and Lee Schalop, Oncoceutics aimed from the start to advance its lead cancer drug from the laboratory to the clinic in as cost-efficient a way as possible.

WHAT IT'S LIKE TO BE A *TRUE* VIRTUAL BIOTECH

The company operated on a virtual basis for its first two years following its founding in 2012. There was no pricey office space, no proprietary labs, and no expensive contracts with consultants or CROs. During this initial growth phase, the company operated with a staff of just four, all of whom had multiple responsibilities, drew modest salaries, traveled frugally, and focused on maximizing the impact for every dollar spent. Indeed, they got things done mostly by getting their hands dirty themselves. For example, Lee Schalop, M.D., chief business officer and cofounder of Oncoceutics, explains, "Our Chief Development Officer designed the drug synthesis method. I served as bookkeeper and configured the e-mail system, and the CEO wrote the copy for the website which the Associate of Research designed and took live." In short, the company, with a burn rate of less than $1 million per year, operated like a typical tech startup rather than a typical biotech startup.

Despite limited financial resources, Oncoceutics, operating in startup mode, was able to satisfy the requirements necessary to open an IND (Investigational New Drug) during these first two years. The company oversaw the manufacture of the drug substance (to required standards) by Chemspec-API and capsules by Frontage Laboratories, both in local facilities licensed by the FDA. It also worked with academic partners who undertook preclinical testing. In addition, it finished the standard safety-testing regimen by partnering with Calvert Laboratories, another local company that took equity in partial payment for toxicology studies.

In its third year of operation as Oncoceutics entered clinical trials, it stepped up its spending but stayed true to its founding philosophy of careful financial stewardship. "We leased an actual office, but it was a single room in incubator space at Philadelphia's University City Science Center," Schalop says. "There we knew we would benefit from being part of a biotech ecosystem — and do so at a low cost." Salaries increased to reflect a heavier workload and the travel that comes with implementing multiple clinical trials simultaneously, but the emphasis remained on compensation driven by stock ownership rather than cash.

THE STRUGGLES OF SEEKING GRANT FUNDING, COLLABORATIONS

Running such a low-cost operation has had its challenges. Aside from keeping everyone motivated with the limited funds available to accomplish multiple tasks, the company needed to generate funding from nontraditional sources, primarily grants and payment-in-kind from collaboration agreements, which were not easy to design or manage.

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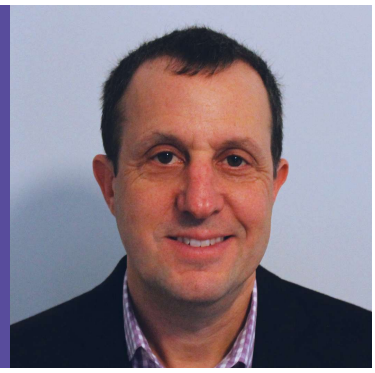
> *"By carefully selecting grant opportunities and working with collaborators to draft applications that met the requirements outlined in RFPs, we achieved a success rate of greater than 75 percent and landed multiple high-value grants."*
>
> **LEE SCHALOP, M.D.**
> Chief business officer and cofounder, Oncoceutics



"Obtaining grant funding required the completion of numerous long and complex applications because the success rate is low, even for the best of proposals," says Schalop. "By carefully selecting grant opportunities and working with collaborators to draft applications that met the requirements outlined in the grant applications, we achieved a success rate of greater than 75 percent and landed multiple high-value grants." Those included difficult-to-get grants like a $1.4 million CURE grant from the Pennsylvania Department of Health and a $1.7 million Fast-Track Small Business Innovation Research (SBIR) grant from the National Cancer Institute (NCI).

Collaboration agreements are often even more tricky and time consuming. Oncoceutics leveraged the relationships of Wolfgang Oster, one of its founders, to identify academic medical centers willing to carry out the necessary lab work because they were focused on publishing their findings, not maximizing profit. Centers including Fox Chase Cancer Center in Philadelphia, Rutgers Cancer Institute of New Jersey in New Brunswick, Dana-Farber Cancer Institute in Boston, and University of Texas MD Anderson Cancer Center in Houston all entered into agreements with the company. While each arrangement is different, all of these centers have agreed to cost-saving structures, such as investigator-initiated trials, to minimize the cost to Oncoceutics. As a result, even with multiple Phase 2 trials underway, the company's corporate overhead remains less than $2 million per year.

A unique collaboration agreement with the University of Texas MD Anderson Cancer Center is a case in point. The agreement covers clinical trials of Oncoceutics' lead drug ONC201 in specific types of blood cancer. Under the nontraditional alliance, Oncoceutics and MD Anderson shared the risk and potential commercialization of ONC201, with MD Anderson receiving a royalty on any eventual sales in lieu of the usual payments for conducting clinical trials.

This was far from easy. Executing the complex agreement with a large institution like MD Anderson Cancer Center took Oncoceutics almost a full year. "The agreement also made the operating procedures for clinical trials much more complicated than usual, which took us off guard," Schalop explains. "For example, obtaining approval from the IRB (Institutional Review Board) took longer than usual because MD Anderson wanted an outside group to review the clinical trial in order to ensure patients' interests were protected." Despite the delays, Oncoceutics felt the outcome was worth the wait. This unique deal, the first of its kind for MD Anderson, provided Oncoceutics with an ONC201 clinical trial led by a world-renowned cancer center without the use of investor cash. In addition, this alternate funding model provided the company with invaluable external validation.

NOT YOUR STANDARD WAY OF BUILDING A BIOTECH

In contrast to the model of low costs and emphasizing grants and partnerships in lieu of equity, the typical venture-backed, early-stage biotech company builds an organization with separate scientific, laboratory, medical, intellectual property, regulatory, legal, business development, finance, and administrative functions. Such a company's standard approach would be to lease office space as well as laboratory space and spend at least $20 million for a staff of 12 to 15 people in order to complete an IND application. A fully-staffed company using this traditional business model typically has a burn rate of more than $10 million a year.

While the Oncoceutics' model remains uncommon in the biotech space, similar companies are increasingly funding themselves primarily through grants and partnerships. An example is Integral Molecular, which is also located in the University City Science Center, next door to Oncoceutics. Founded by a University of Pennsylvania scientist who licensed technology from the university, the company, which is developing a pipeline of therapeutic antibodies for under-exploited membrane protein targets, recently received $9 million in NIH funding and works with over 100 different pharmaceutical and biotechnology customers and partners, which has allowed it to grow and operate without outside investment.

According to Schalop, "Obtaining selective grants and forging partnerships with academic institutions have allowed us to advance our lead compound toward commercialization with a remarkably small amount of equity." Going forward, it is likely that more and more early and mid-stage companies in the biotech space will choose to do the same and avoid the limitations of the traditional venture-backed model by combining grant funding, creative partnerships, and limited amounts of equity to fund their growth. L

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Bio

How Purdue Pharma Hopes To Use The Apple ResearchKit

ED MISETA Editor Clinical Leader @EdClinical

With the continuing effort of many in the industry to bring mobile and wearable technologies to patients, Larry Pickett, CIO for Purdue Pharma, is quick to note that no one has all the answers. Although many in the industry will always seem anxious to jump on the latest technology wave, no one can accurately predict where it will eventually end up. "When the iPad first came out, there were very intelligent technology people who said consumers would never adopt it," he says. "They could not have been more wrong."

Few seem to doubt that mHealth technologies will pave the way to more efficient trials and a better patient experience. But as with any new technology, someone still has to be the pioneer to prove its viability in a clinical trial. Purdue Pharma is attempting to do just that by evaluating the use of the iPhone, Apple Watch, ResearchKit, and various healthcare apps for patients suffering from pain.

ResearchKit is an open source framework that was released by Apple last year. Using sensor technology specifically associated with the watch, developers can use the API to create apps that will allow sponsors to track, collect, and record data based on a multitude of measures.

There are three customizable modules for companies interested in conducting clinical trials: The survey module collects patient information, the consent module captures the patient's consent and shares information about the trial, and the active task module tracks patient activity levels. The latter features voice capture, which may allow physicians to detect pain levels based on the speaking patterns of the patient. For certain conditions, the speed at which information is entered into a device can also be indicative of patient pain levels.

"We are particularly interested in the Apple Watch as a sensor device not because of what it can do today, but the potential it holds for the future," notes Pickett. "When I look at the watch today, it may not have features that would compel me to buy and wear one. But we know it will be improved over the years and continue to gain additional capabilities. Today it might measure heart rate and activity levels. But there is a huge potential for the watch to eventually allow us to better connect with the patient experience. We may soon be able to use it to remind patients to take their medication or communicate pain levels to a physician. It's that potential that has us evaluating it as a game changer in the clinical space."

BETTER PATIENT-REPORTED OUTCOMES

Purdue is attempting to use Apple technology to give patients the opportunity to communicate their pain levels over a long period of time. Pickett believes this is a critical feature, as it will enable a physician, looking at a portal, to know how patients are feeling and what their pain trends are before they ever step foot in the office. In the past, a physician might know only how patients felt the morning of their visits, but not see those pain levels over a lengthier period of time. Pickett notes there may even be a role for gamification (the mixing of entertainment with self-monitoring) to help patients set goals for their health and wellness while providing feedback.

"I see many benefits coming from this technology," notes Pickett. "First, there is information being supplied remotely from patients to physicians over a long period of time. There is also the opportunity to correlate that information with factors such as sleep, activity levels, or heart rate to determine connections between them. There is also a good opportunity for patient engagement. There is anecdotal evidence noting that if you can engage patients in the management of their own health, they are more likely to take ownership of it. I think we will see more of that in the future."

While the opportunities are promising, Pickett notes there are some disadvantages to the Apple Watch. One is that the battery life is very short and typically has to be charged every night. Cost is also a concern. The watch has to be paired with an iPhone for certain capabilities such as GPS. In an effort to scale up the use of the technology in trials, the use of both devices could become prohibitive. Many patients would not be able to afford an Apple Watch or iPhone, which would require the sponsor to absorb the cost of supplying them. "We will likely fund a study that will provide the devices so as to learn more about them in a limited way, but I do have concerns about that cost going forward," Pickett says.

Because of both of these issues, Purdue is looking at other devices, hoping there might be a companion product that patients could wear. For example, someone wearing an Apple Watch to monitor pain might also wear a $30 device to monitor their sleep. Pickett notes some of these devices, such as the Misfit, have a six-month battery life, are small and light, and are more comfortable to wear to bed.

ARCHITECTURE IS IMPORTANT

One vital consideration to incorporating mobile technologies into a trial is deciding on the appropriate information to capture. Having that knowledge also will help with understanding how the technology can best impact the lives of patients. According to Pickett, that is why Purdue is performing this investigative work. "We have to make an impact on the lives of patients, improve their outcomes, and reduce their pain," he notes. "The key to doing that properly is studying the tools that are available, deciding what information is the most important, and providing patients with the tools [phones, watches, and apps] to make it happen. Then we can take what we learn and keep improving the process going forward."

Pickett is convinced that Purdue will have no problems with either the watch

or the phone; he says those technologies are pretty straightforward. But getting the information to the portal or the EHR (electronic health record) does require additional expertise. Therefore, it is necessary for them to partner with technology companies to enable those capabilities. Purdue would still be very much involved in mapping things out.

"Without getting into an overly technical discussion, our architecture integrates between the phone and the watch using various servers and technologies," he says. "It is not that complicated, and it does not take long to do. For example, I know of one developer who got the ResearchKit when it came out and churned out an application in just four weeks. If you know Swift or Objective C (two programming languages) it is not that difficult. But you really need to put some thought into the architecture you put in place, especially in terms of where you collect and store the data and how it will move between those locations. What we are most interested in is how the information will get into the physician portal and then ultimately into an EHR."

One innovative idea is for patients to actually have access to their EHR. They would be able to see it and actually monitor and edit some of the data. At this point it is not clear how that might be done, but Pickett notes it is something researchers are discussing. It's certainly an innovative idea that would empower patients by giving them ownership over their data.

TWO POTENTIAL APPLICATIONS

Pickett notes there are two projects being examined at Purdue, but stresses at this time nothing has been finalized. One involves the use of an iPhone app, while the other looks to incorporate the Apple Watch.

With the Apple Watch, there is a small amount of space to work with. Therefore, anything involving the watch should be kept simple. Indicating pain level is one option being examined. By pressing a plus or minus button, patients can increase or decrease their current pain level and then record it. The information will go from the watch to the iPhone to the EHR portal. Additional measures, such as the patient's heart rate, could also be recorded.

With the iPhone app, patients would learn how the study works, register their information, complete surveys, and perform informed consent. The iPhone also allows for the sharing of a short video or slideshow to provide additional information about the device, the study, and how information will be transferred.

Questions asked in the survey might include age, sex, where they live, and any other information that would qualify them for the study. If a patient is eligible, they could then enroll and start recording their pain levels via the phone. One of the options being evaluated is showing patients a rotating 3D image of the human body. By simply tapping on the phone, individuals are able to indicate where pain exists. By tapping multiple times, they are able to increase the severity level of the pain.

"We also feel it might be helpful to try and correlate a person's pain with their activity level, as measured by their number of daily steps they take," says Pickett. "The pain level is a patient-reported outcome, and what the patient is feeling is certainly subjective, but what they have to say is valuable and important. Over a period of time, be it weeks, months, or years, there are good insights that could be derived from this data."

The use of this app does raise a few concerns, which Purdue is evaluating. One is adverse events. If patients feel they have experienced an adverse event, Purdue would like a quick and easy method for them to report it. Pickett notes they are evaluating the option of having patients click on a button and be automatically connected with either a physician or nurse practitioner.

A second concern is data privacy, which Pickett describes as absolutely critical to any study. For that reason, he likes the idea of patients having control over their data, including the ability to delete the information if they decide to do so, although he stresses that this is his personal opinion, and that it may, in fact, not be compatible or permissible in a clinical trial.

Medication reminders are also being evaluated. Pickett states they are an important in any pain study. "If a patient is feeling really good, it's possible they will forget to take their medicine. Oftentimes they will not remember to do so until the pain suddenly gets severe in a short amount of time. Sending those reminders once or twice a day can keep the patients taking their medicines on time and prevent those situations from occurring."

NEXT STEPS

At this time, Pickett is feeling very good about his initial assessment of ResearchKit. He notes Purdue has (fairly quickly) developed a proof of concept application for both the iPhone and the watch. The company is also discussing with a partner the best method to transmit the data into a portal or EHR. The next version of both the watch and ResearchKit will soon be hitting the market, and he is excited about the prospect of additional sensors being incorporated into devices and how his company might be able to use them.

"We think this is just the beginning," he adds. "We still need to figure out how to apply data science and predictive analytics to combine the data we will be collecting with other data sets that may be available. There is a lot of data integration that will have to happen, and we are in need of new techniques for doing that. They need to be visual, they need to be easy to search and retrieve, and they need to tell us things we do not already know. We will have to do this in a smart way in order to make it pay off for both pharma and all of our patients."

"We are particularly interested in the Apple Watch as a sensor device not because of what it can do today, but the potential it holds for the future."

LARRY PICKETT
CIO, Purdue Pharma

The Uphill Battle Toward Innovation For Antibiotic Resistance

SUZANNE ELVIDGE Contributing Writer

The discovery of antibiotics as a class of drugs, based on Alexander Fleming's breakthrough in 1928, seemed like a miracle, with potential to rid people and animals of the scourge of bacterial infection. However, by 1947, just four years after the beginning of mass production of penicillin, the first penicillin-resistant strain of staphylococcus aureus *had emerged.*

Because there has only been one new class of antibiotics since 1980, there are key unmet medical needs and therefore, important opportunities for the pharmaceutical industry. But there are also some major challenges to overcome.

UNDERSTANDING THE GROWING CHALLENGE OF ANTIBIOTIC RESISTANCE

According to the U.S. CDC in 2013, antibiotic resistance is the cause of more than 2 million infections and 23,000 deaths each year in the U.S., with costs of $20 billion and productivity losses of $30 billion.

As a response to the increasing levels of drug resistance, the U.K. government has worked with economist Jim O'Neill and the Wellcome Trust to create the Review on Antimicrobial Resistance. Its role is to understand the problems and propose solutions, from both the economic and the social perspective. O'Neill has described the future economic and social costs of antimicrobial resistance as still growing and too great to ignore, with a potential 10 million deaths a year worldwide by 2050, a higher mortality rate than deaths from cancer and diabetes combined. This could mean an economic loss of over $100 trillion. Solving the problem of antimicrobial resistance will be a combination of meeting scientific, economic, and communications challenges, and the pharmaceutical industry will have a key role to play in all of these. While solving or preventing the problem will be a costly process, it is likely to be a fraction of the cost of dealing with the long-term problem of resistance.

THE IMPORTANCE OF PHARMA-ACADEMIC COLLABORATIONS

The pharmaceutical industry and academia play important roles in developing new antimicrobials and preventing the development of resistance in order to improve patient outcomes. The companies working in this space tend to be startups or small to medium enterprises. For example, in January 2015, researchers announced the discovery of teixobactin, the first new class of antibiotics to be discovered in almost 30 years. The antibiotics are in preclinical development with U.S.-based early-stage biotech NovoBiotic Pharmaceuticals. Another early-stage company, Blueberry Therapeutics, is working to develop both new antibiotics and antibiotic resistance breakers, which are small molecules and biologics that target the bacterial-resistance mechanisms and can restore the sensitivity of bacteria to standard antibiotics.

For much of the antibiotic research being conducted, the challenge is bridging the gap between the idea, which is generated by academia or early-stage startups, and approval/market launch. Collaborations between industry and academia can play a role in this process. For example, Redx Anti-Infectives, a subsidiary of U.K.-based startup Redx Pharma, is developing new anti-infectives against methicillin-resistant staphylococcus aureus (MRSA). This is as part of a £5.6 million (approximately $8.3 million) collaboration with the NHS Royal Liverpool and Broadgreen University Hospitals Trust. According to Redx Pharma, which is based at the Alderley Park BioHub along with Blueberry Therapeutics, the company's collaboration is the first example of a type of deal in which the NHS funds development in return for a promise of commercial returns in the future.

Another example of this kind of collaboration is also a sign that Big Pharma is returning to the field. In May 2012, GlaxoSmithKline and AstraZeneca, along with academics and other pharma companies, set up an £180 million

“Solving the problem of antimicrobial resistance will be a combination of meeting scientific, economic, and communications challenges, and the pharmaceutical industry will have a key role to play in all of these.”

($261 million) research collaboration. Part of the European Innovative Medicines Initiative (IMI), the aim of the agreement, dubbed New Drugs for Bad Bugs (ND4BB), is to combat antibiotic resistance in Europe by tackling the scientific, regulatory, and business challenges. In March 2015, the White House cited the program as a potential collaborator in its U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria. Another example of Big Pharma moving back into antibiotics is the collaboration between AstraZeneca and Forest Laboratories to develop the combination antibiotic ceftazidime-avibactam, currently pending approval in Europe for in-hospital use.

BATTLING ANTIBIOTIC RESISTANCE THROUGH DIAGNOSTICS

According to a Health Protection Agency survey in 2011, around a quarter of patients believed that antibiotics work on coughs or colds, and over half of patients expect to be prescribed antibiotics for a respiratory tract infection. In a brief and pressured consultation, it may be difficult for healthcare professionals to explain to patients, parents, or caregivers why they should not be given antibiotics, and perhaps as result of this, 97 percent of people in the survey said that a healthcare professional put them on antibiotics when requested.

Diagnostics and personalized medicine will be important in the battle to reduce the development of resistance, as this approach will support doctors or pharmacists when they turn down requests for antibiotic prescriptions for people with viral infections. This approach will also ensure that the right antibiotics are given to people who need them. To reach this goal, the diagnostics will need to be simple, low-cost, fast, and usable at the point-of-care. In the U.K., some Boots pharmacies are offering a Sore Throat Test & Treat Service. An initial consultation with a health advisor assesses whether the infection is likely to be bacterial or viral. For those that show signs of being bacterial, a pharmacist carries out a further examination and offers a throat swab test to detect Streptococcus A, and only offers antibiotics if this is positive.

Spectromics, using spectrometric technology from the University of Manchester, has developed a fast and accurate point-of-prescription test. This monitors reactions between the patient sample and a panel of antibiotics to diagnose whether a bacterial infection is present or not. It identifies antimicrobial susceptibility and resistance and then suggests the best form of treatment. The solution has been launched in India for the diagnosis of tuberculosis. Epistem, which also has its roots in the University of Manchester, has created a rapid and low-cost molecular diagnostics platform called Genedrive, which has been approved and launched in India for the diagnosis of tuberculosis. The key challenge for diagnostics, however, will be justifying the cost of a test when a course of antibiotics can cost less than a dollar.

EDUCATION IS A BIG PART OF PREVENTION

Preventing bacterial infections has potential to reduce the number of visits to doctors, therefore reducing the numbers of requests for antibiotics. The route to prevention can include education for patients, for example basic hygiene hints and tips to prevent spread of infection, explanations about the infections (both bacterial and viral) where antibiotics don’t help, and reminders about how to take antibiotics correctly, including finishing the treatment course. Doctors need to be supported by tools and information to help them when working with patients who are requesting (or even sometimes demanding) antibiotics. In a trial carried out in collaboration between England’s Chief Medical Officer, Public Health England, the U.K. Government’s Department of Health, and the Behavioural Insights Team, English general practitioners (GPs) were sent a letter that provided feedback on their antibiotic prescribing practices. In the study, the GPs with the highest antibiotic prescribing rates cut antibiotic prescriptions by 3.3 percent over 6 months. While this may not seem like a lot, it equated to 73,000 fewer prescriptions and direct savings of over £92,000 (around $131,000). According to the Behavioural Insights Team, it’s a simple intervention and should cost only around 6p (less than 9

British Chancellor of the Exchequer George Osborne visits Redx Anti-Infectives laboratory at AstraZeneca's Alderley Edge site in Cheshire, England. Photo credit: www.jonparkerlee.com

cents) per prescription saved. In contrast, a patient-focused education campaign didn't have a significant impact on prescribing rates. Education and support schemes like this should be supported by the pharmaceutical industry.

Vaccines have been highly successful in preventing viral infections and have a growing role in the prevention of bacterial infection and therefore potentially reducing the demand for antibiotics. GlaxoSmithKline acquired vaccine specialist GlycoVaxyn in early 2015, along with a small pipeline of early-stage vaccines against pneumonia, Pseudomonas, Staphylococcus aureus, and shigellosis.

Da Volterra is taking a different approach to prevention. Based in Paris, France, Da Volterra is a clinical-stage biotechnology company with a focus on the microbiome. Its lead product, DAV132, is designed to prevent the occurrence and recurrence of antibiotic-associated Clostridium difficile diarrhea. It is co-administered with antibiotics and captures residual antibiotics in the late ileum, caecum, and colon before they can disrupt the intestinal microbiota.

THE UNAPPEALING NATURE OF ANTIBIOTIC DRUG DEVELOPMENT

Drug development is a costly business, and drug companies need to be confident of a return on investment. The increasing (and necessary) push toward appropriate use of antibiotics and the low price of the existing marketed drugs means an uncertain payoff for pharmaceutical companies and investors. Therefore, it's an unattractive investment profile, making it difficult to see an economic argument for developing a drug that should be prescribed only under very specific circumstances and for as short a period of time as possible — even less so for developing an antibiotic of last resort. This is true for small companies struggling to gain initial funding, companies developing innovative nontraditional approaches (e.g., bacteriophages, antibodies, or d)rugs designed to "break" resistance) and for larger companies that need to show a return on their investment for shareholders.

Changing this mindset requires a change in the economics and the development of a robust commercial model, based on both push and pull mechanisms:

PUSH

- Public and government buy-in to create an environment to fund innovative drugs and technologies
- Creation of public-private, academia-industry, and intra-industry partnerships
- Establishment of centers of excellence

PULL

- Rewarding physicians for appropriate use and stewardship in developed and developing countries
- Developing new pricing and reimbursement models
- Patent pause (the ability to pause patent life and development at Phase 2 and then accelerate when needed); patent vouchers and orphan drug-style patent extensions
- Underwriting of R&D costs by governments
- Tax credits for companies working in antimicrobial resistance

One of the key approaches to enticing companies to invest in this area will be the development of better pricing models. This could include value-based pricing, which is more akin to the high prices charged for drugs for rare diseases. Value-based pricing would provide return on investment, as well as reduce demand through payers and people who pay or co-pay for their own medications. However, these prices would need to be subsidized for certain patient groups and for developing countries. Risk-sharing agreements between healthcare institutions and pharmaceutical companies could also help balance risk.

THE FUTURE OF ANTIMICROBIAL RESISTANCE

Preventing and combatting antimicrobial resistance is a challenge for the pharmaceutical industry, from startups to major global players. Finding a solution will be dependent on collaboration and a constellation of incentives, including funding, pricing models, and optimization of FDA and EMA regulatory pathways to bring drugs and other solutions through clinical trials and on to the market to the patients who need them. L

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The Value Of A Dual-Track Process For Raising Capital

ALEX CASTELLI

Alex Castelli is the technology and life sciences industry practice leader at accounting, tax, and advisory firm CohnReznick LLP. Castelli also coleads the firm's National Liquidity and Capital Formation Advisory Group. He can be contacted directly at alex.castelli@cohnreznick.com.

Through the first half of 2016, market volatility has continued, and both IPO and M&A transaction activity is down in the middle market when compared to each of the previous two years. Until some stability returns to the capital markets, life sciences companies may find it more challenging to complete a capital-raising transaction.

When stability does return to the capital markets and investors become more confident, life sciences companies with an interest in raising capital may want to create a competitive buzz surrounding their prospective offering, referred to as "friction" in the investment banking community. Creating competitive friction is largely the function of the seller and the seller's investment banker in an M&A process. The intent behind creating competitive "friction" is to maximize the purchase price of the deal. In addition to creating friction between groups of potential private investors, the same can be accomplished when a company pursues an M&A transaction and an IPO at the same time — the dual-track process.

So often thought of as an exit strategy for private equity firms, the dual-track process can certainly be utilized by life sciences companies that are considering raising capital by selling equity. The dual-track process involves pursuing both an IPO and a private-sale process simultaneously. As both transactions progress, one will emerge as the best to meet the needs of the company and its shareholders.

Even though the dual-track strategy is typically most effective when the IPO market is more vibrant than it has been recently, life sciences IPOs, albeit fewer, still seem to be finding their way through the pipeline. So the dual-track process remains a viable option for life sciences companies to consider.

ADVANTAGES OF THE DUAL-TRACK PROCESS

- A more competitive sales environment (referred to as an auction process by investment bankers). If the life sciences company discloses that it is pursuing both an IPO and an M&A transaction simultaneously, this may lead to a more competitive auction process driving up the company's purchase price.

- Increasing speed to respond and close the deal. Pursuing a dual-track process could encourage private investors to be more responsive and increase the speed to close, as they are competing against the timeline of the IPO.

- From an efficiency perspective, life sciences company management teams can utilize diligence and other materials from the electronic data room to satisfy the needs of both transactions.

- To most companies, the process of preparing a company to go public will require improvements to governance, internal controls, and financial management and reporting. Even though these improvements will be implemented to prepare for the planned IPO, private buyers will find them to be attractive selling features.

- A seller never knows when market factors impacting IPO or M&A activity may change to their benefit or detriment. Pursuing a dual-track introduces additional flexibility and removes the temptation to time the market. Be mindful that a life sciences company's ability to achieve certain milestones in accordance with their strategic plan can either help or hurt an IPO or M&A transaction.

- The seller can delay a final decision until after all of the benefits and pitfalls of both transitions have been exposed.

In addition to the above referenced advantages, the "testing the waters" and "confidential filing" provisions of the JOBS Act, both used by almost all life sciences companies to go public, although not intended to directly support a dual-track process, have done just that. Thanks to the "testing the waters" provisions of the JOBS Act, life sciences companies can communicate with investors earlier in the IPO process and with a greater flexibility, gathering valuable intelligence that could help bolster their negotiating position with private investors. And as a result of the "confidential filing" provisions of the JOBS Act, it has become easier to pursue a dual-track process without publicly revealing information during the IPO process that may be beneficial to a buyer involved in the M&A process.

CONSIDERATIONS FOR MANAGEMENT

To maximize the value of the dual-track process, the life sciences company's management team must be prepared to exercise a certain degree of flexibility

“The dual-track process can certainly be utilized by life sciences companies that are considering raising capital by selling equity.”

concerning the outcome of the process. After all, when the process begins, the management team may not know whether a public or private entity will emerge when the deal is done. The management team must believe in the company’s ability to survive and thrive as either a public entity or a private company.

Even if the management team can become comfortable with this aspect of the dual-track process, there are several other aspects that require thought and consideration.

- A dual-track process is far more costly than pursuing either an IPO or an M&A transaction.
- Running a dual-track process will consume more of management’s time. Remember, unless management feels comfortable in their ability to run two parallel processes, as well as focus on the day-to-day operations of the business, they should consider another option.
- If the shareholders of the life sciences company desire an immediate exit posttransaction and as a result of the dual-track process, an IPO is issued, the deal may not satisfy the desires of the shareholders.
- Getting stuck with a form of capital or a relationship that does not match the strategic plans of the seller could be detrimental to the growth of the company.
- Management will need to be skilled communicating with different investors, who will each have different sets of expectations and requirements.

As with any capital-raising endeavor, it is important to weigh all of the risks and rewards associated with the final disposition of the deal. The characteristics or personality of the best-fitting form of capital will be those that fulfill the strategic needs of the company. In a sluggish IPO and M&A market, life sciences companies may be unique in their ability to pull off a successful dual-track process. Because even though overall equity transaction activity may be lagging, investors continue to view life sciences companies as worthy investment options. L

Increasing Self-Awareness In Our Leadership To Drive Organizational Success

TANVEER NASEER, MSC.

There's no question that today's leaders are facing increasing demands on their time, attention, and resources as well as rising pressure levels in which to perform.

No doubt this is why there's been a growing interest in how leaders can increase their self-awareness. As such, I'd like to share the following three steps that every leader can employ in order to increase their self-awareness about how they lead their employees.

1 SCHEDULE TIME IN YOUR AGENDA FOR REFLECTION

If there's one thing all of us are familiar with in today's fast-paced work environment, it's that if you don't schedule time in your workweek to do something, it's not likely to get done. That's why the first and most important step in the process of increasing our self-awareness is regularly scheduling time for reflection and review.

Granted, it can seem like a luxury when we consider the numerous demands on our time and attention. However, you need to remind yourself that the reason you're doing this is to help you become more effective in how you lead your team and organization.

2 REMOVE DISTRACTIONS FROM YOUR SURROUNDINGS

When the time comes for us to begin reflecting on our leadership, it's important that we make sure we remove all distractions from our surroundings. That means turning off smartphone notifications, closing our computer screens, and muting our phone.

Again, thanks to today's 24/7, always-on digital environment, it's very easy for us to get caught up in what's going on around us. But we have to remember that what's key to our ability to succeed is making time to better understand whether we are providing the right conditions to bring out the best in those we lead. So give yourself that space to focus on you and how you can be a better leader.

3 CREATE A LIST OF QUESTIONS TO BEGIN THE REFLECTION PROCESS

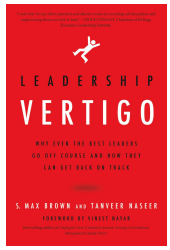
So now that we've dedicated time for reflecting on our leadership and have created a space that frees us to focus on ourselves, the next thing we need is a road map to help guide us through this process of increasing our self-awareness.

The way to do this is by writing up a list of questions that will help you reflect on your leadership and what it's really like to work under you. It's important, though, that these questions involve some deep introspection, as the answers are not as obvious as we might think they are. Here are some examples to help give you an idea of the kinds of questions you need for this step:

- How did I react when issues were brought to my attention?
- How aware am I of the emotional states of those around me?

Although these steps are pretty straightforward, when put together they become a powerful tool that will help you to better understand how you show up as a leader in your organization, by increasing your self-awareness about the way you lead.

Tanveer Naseer is an award-winning, internationally acclaimed leadership writer, keynote speaker, and author of *Leadership Vertigo*. Read more of his writings on leadership and management on his award-winning leadership blog at TanveerNaseer.com.



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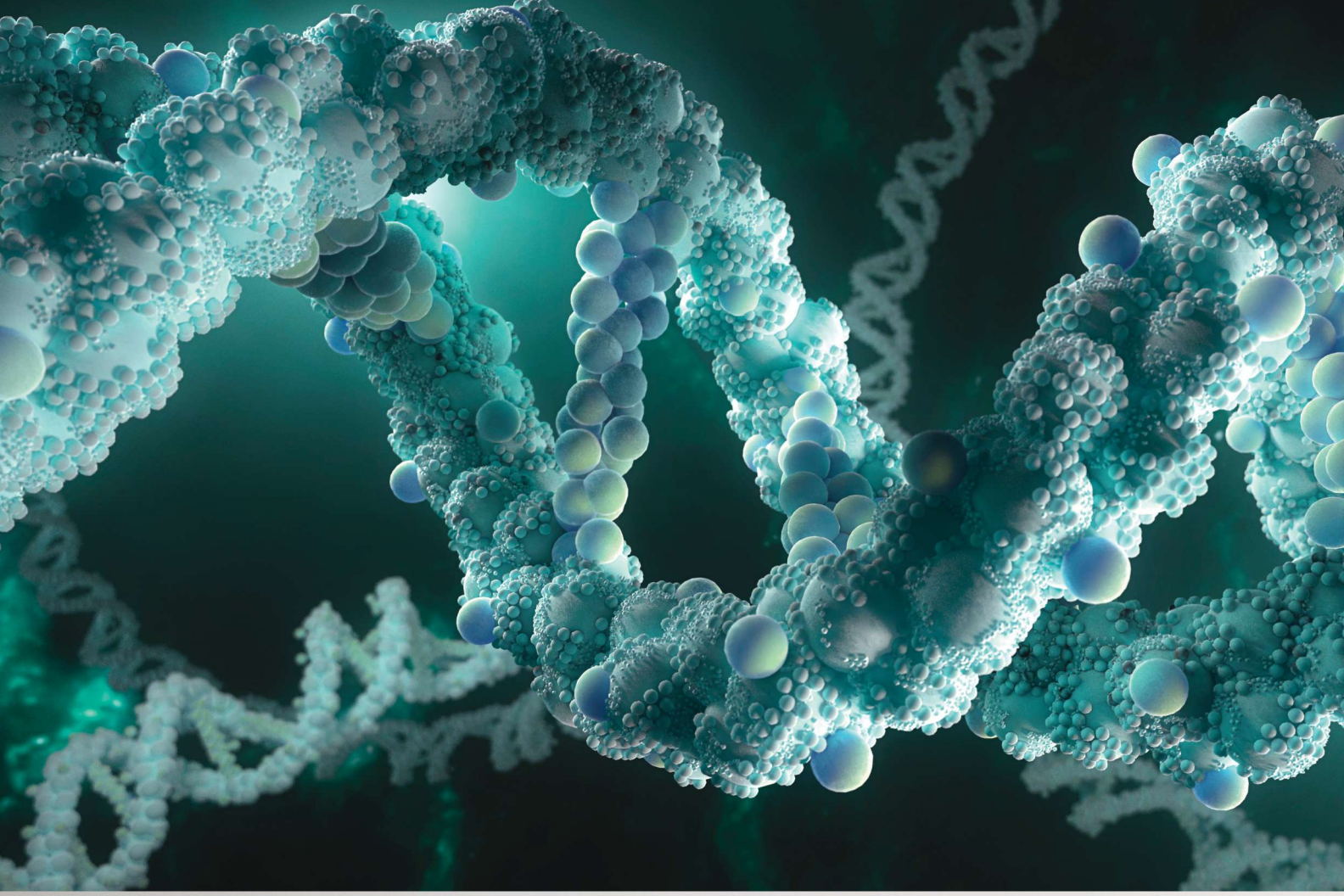

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