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The Rocky Journey to Refocusing BioMarin

Recognized today as one of the world's most-innovative companies, it was a far cry from that 12 years ago when Bienaimé took over. **p. 14**

JEAN-JACQUES BIENAIMÉ
Chairman & CEO
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14 Cover Story: BIOMARIN

Recognized today as one of the world's most-innovative companies, BioMarin was a far cry from that 12 years ago when Jean-Jacques Bienaimé took over.

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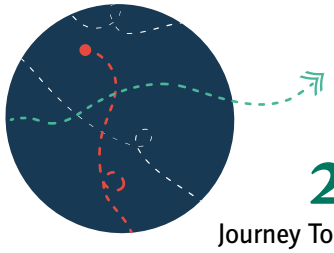

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Do You See A Trend In *Life Science Leader*?

ROB WRIGHT Chief Editor

Having Jean-Jacques (J.J.) Bienaimé, chairman and CEO of BioMarin Pharmaceutical, on our cover this month represents a recent trend happening at our magazine — we're interviewing more and more CEOs and presidents.

We have always focused on interviewing top biopharma executives, but that doesn't always mean the person at the top of the org chart is the right one for a story. For example, if investigating how a company implemented a new manufacturing efficiency process, the COO or some other manufacturing executive may be a better fit than the CEO. Still, we have featured a string of CEOs recently — CSL Limited's Paul Perreault (February), Grünenthal Group's Gabriel Baertschi (March), Vivek Ramaswamy from Roivant Sciences (April), and now Bienaimé. And it looks like this trend is going to continue.

One of the articles I'm working on for our June issue involves Juan Ramón Alaix, CEO of Zoetis (NYSE: ZTS), which is one of biopharma's biggest ($2.2 billion) IPO spinoffs. That fact, along with some internal data indicating our readers were very interested in the animal health field, put Alaix high on our list of executives to interview. We wanted to know how Zoetis has managed to live up to its IPO expectations, reaching a current valuation of approximately $26 billion with annual sales revenues of nearly $5 billion. To give you some perspective, if ranked among top 25 biotechs, Zoetis would be in the top 15 and bigger than the likes of Alkermes, Mylan, and Valeant, just to name a few. Luckily, I was able to meet Alaix following the Zoetis breakout session at this year's J. P. Morgan Healthcare Conference in San Francisco. Our dialogue has continued these past few months and will culminate with the article in the June issue.

Another project in the works involves a group of "retired" biopharmaceutical industry CEOs. What insights might six former CEOs — no longer constrained by corporate lawyers and company PR teams — have for today's industry leaders? A lot. After all, most former biopharmaceutical CEOs find it very difficult to actually retire; their wisdom is always in high demand. Combined, these industry icons serve on over 34 corporate and nonprofit boards and are highly involved in a variety of other projects. The group includes past chairs of our industry's largest trade associations (BIO and PhRMA), and we look forward to sharing their perspectives in our upcoming July issue.

Will this trend of CEOs on our cover continue? I hope so, but it's hard to say. What I can attest to is LSL's continued commitment to engage with industry leaders willing to share their best business practices. And, as always, we welcome your feedback as to what top execs you would like to see featured. Have a suggestion? If so, email me at rob.wright@lifescienceconnect.com, or better yet, give me a call at (814) 897-7700, ext. 140. We look forward to hearing how we can continue to improve *your* magazine to better serve you — our readers.

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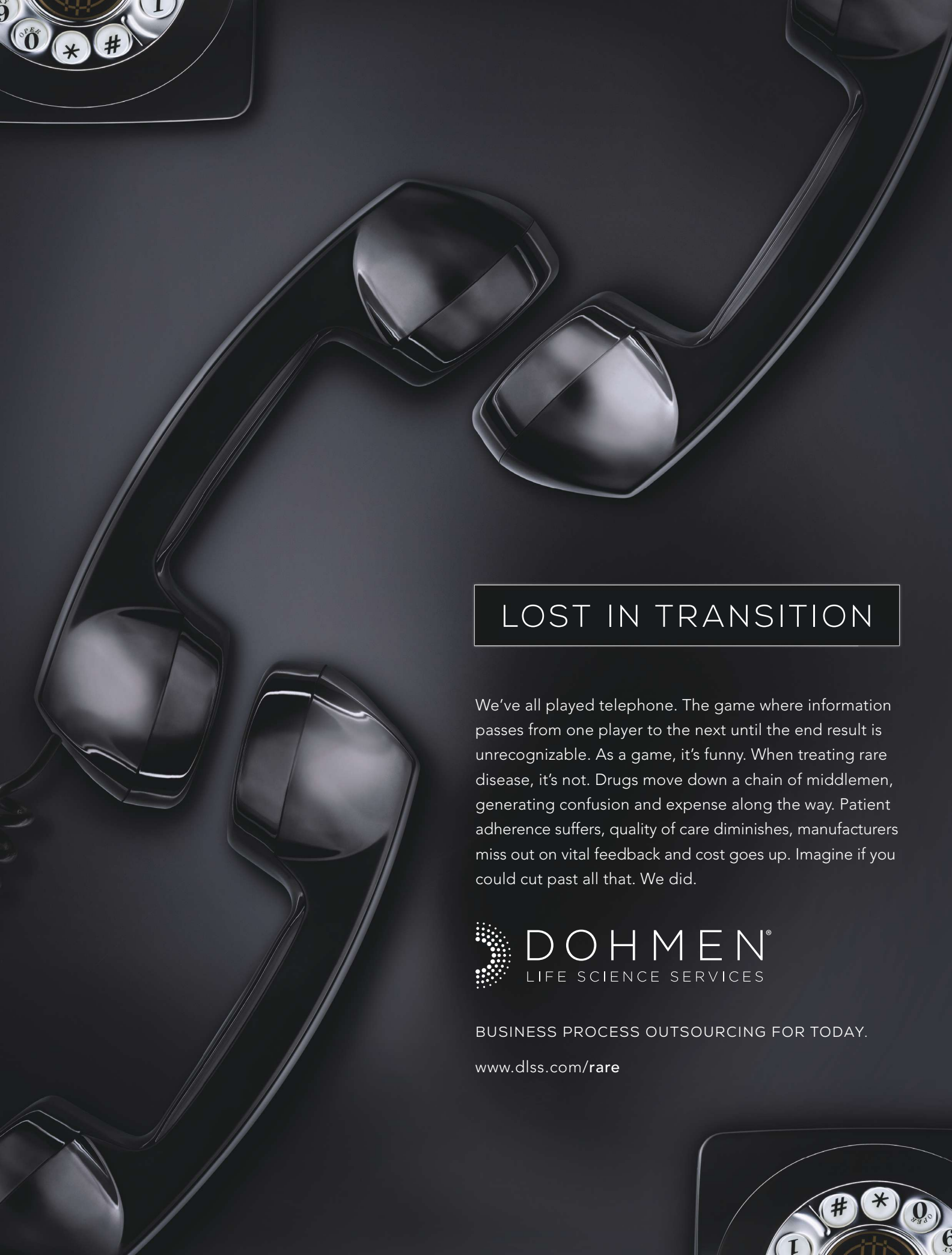

LOST IN TRANSITION

We've all played telephone. The game where information passes from one player to the next until the end result is unrecognizable. As a game, it's funny. When treating rare disease, it's not. Drugs move down a chain of middlemen, generating confusion and expense along the way. Patient adherence suffers, quality of care diminishes, manufacturers miss out on vital feedback and cost goes up. Imagine if you could cut past all that. We did.

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Q What do you see as the best opportunity for industries (within healthcare) to collaborate and solve big issues?

A THERE IS AN URGENT NEED to improve patient access to medicines. This subject has devolved into recurring cycles of finger pointing among various sectors within the industry, including PBMs, distributors, hospitals, biopharma and generics companies, pharmacies, and others. The truth is that all these sectors take a percentage of the list price of medicines and therefore exert upward pressures, directly or indirectly, on pricing, while high insurance co-pays excessively limit patient access to medicines. All the parties must collaborate on solutions that enhance patient access while still incentivizing drug innovation. An example is Value Based Arrangements, which are nascent and need to be accelerated. We need leadership from CEOs and boards of the larger, more influential companies, whose examples would then be followed by others. Such leadership must also assert itself within the other sectors, as well as more broadly across the biopharma industry.

RON COHEN, M.D.
is president, CEO, and founder of Acorda Therapeutics, Inc., a public biotech company developing therapies for spinal cord injury, MS, and other nervous system disorders.

Q What can be done to improve gender balance in the boardroom?

A STUDIES DEMONSTRATE GENDER-BALANCED BOARDS have improved shareholder value, good corporate governance, better decision making, and a more positive corporate image. Some of the ways to increase the number of women on boards include:

1. Share the business case for change – this goes beyond the "right thing to do" to being a business imperative.
2. Demand executive recruiters bring a balanced slate – having at least two women increases the chance that a woman is the final candidate.
3. Ensure your board and C-suite sponsor women – the primary route to the board room is through a recommendation.
4. Encourage women leaders in your organization – supporting the advancement of women will provide you greater talent at all levels.
5. Leverage and celebrate your company's efforts – visibility as an industry leader gets positive coverage and contributes to attracting and retaining top female talent.

LAURIE P. COOKE, BS, RPH, PGDIP, CAE
is the CEO of the Healthcare Businesswomen's Association (HBA), a global nonprofit professional association.

Q What U.S. government initiative do you think has proven most beneficial to sparking innovation in the drug industry?

A THE TRANSFERABLE NEGLECTED TROPICAL DISEASE FDA PRIORITY REVIEW VOUCHER (PRV) is probably the most important government initiative to stimulate investment in diseases affecting billions of patients in developing countries. The ability of a large company to purchase such a voucher for use on a potential blockbuster drug in an indication otherwise ineligible for priority review can catapult an asset well ahead of its competitors. The ability of a small, cash-poor company to sell the voucher to a larger firm developing that blockbuster drug can provide a financial benefit independent of the commercial risk of neglected diseases products. It's a win-win for seller and purchaser. Issuance of many Rare Pediatric Disease PRVs, a sister program, has now increased supply and depressed sales price of PRVs in the last year, which is unfortunate.

CAROL NACY, PH.D.
is CEO of Sequella, Inc., a private company that develops new anti-infective drugs.

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Provider Consolidation Raising Costs And Undermining Competition

JOHN MCMANUS The McManus Group

As Republicans attempt to recover from their face-plant on repealing and replacing Obamacare, policymakers are grappling with how to address the growing problem of healthcare provider consolidation, which appears to be raising costs and undermining competition.

Together, hospital and physician services account for more than half of national health spending, and their finances are increasingly intertwined. Hospitals recently embarked on a buying spree of physician practices. According to *Forbes*, the number of hospital-employed physicians increased 50 percent from 2012 to 2015.

This has sent ripples through the healthcare system, as hospitals seek to recoup these investments that typically far exceed the value of services the acquired physicians could possibly bill. According to the Medical Group Management Association, losses of $200,000 per hospital-employed physician are not unusual. Hospitals make up this loss by capturing highly profitable in-house imaging, laboratory services, and drug administration.

A 2015 Government Accountability Office (GAO) study found Medicare pays hospitals about twice as much for administering drugs than freestanding physician practices. Couple that windfall with the 340B revenue that many nonprofit mega-hospital systems can derive by acquiring drugs at substantially discounted prices and then providing them to both insured and uninsured patients at market rates, and it's any wonder that independent physician practices can compete.

According to the Berkeley Research Group, sales to 340B doubled between 2010 and 2015 and expanded by 66 percent between 2012 and 2015 alone. Notice the correlation between physician practice acquisition and 340B expansion? GAO concluded that the sizeable margins 340B hospitals realize on the statutorily discounted drugs have contributed to higher utilization of Part B drugs. The 2016 Medical Pharmacy Trend Report from Magellan Rx Management noted hospitals that use the percent-of-charges approach allows them to be paid about twice as much as physician offices. When combined with 340B, this delivers 70 percent profit margin!

The migration of physicians to salaried employment at hospitals theoretically mitigates physicians' incentives to increase utilization and also offers the potential for coordinated care. But the reality is that salaried employment actually increases health costs:

- The Medicare Payment Advisory Commission (MedPAC) observed Medicare paid hospitals $1.8 billion more for routine evaluation and management (E&M) services provided by their employed physicians than physician office rates in 2015.
- A recent JAMA study that examined 7.4 million Medicare beneficiaries in 240 metropolitan areas from 2008 to 2012 concluded outpatient costs increased for hospital-acquired physician practices by $500 million.
- Similar results were found on the commercial side; a University of California, Berkeley study that reviewed 4.5 million commercial HMO enrollees found hospital-owned organizations incurred 19.8 percent higher expenditures than physician-owned organizations for professional, hospital, laboratory, pharmaceutical, and ancillary services.

Congress took a modest step in the Bipartisan Budget Act of 2015 to stop the bleeding by prohibiting the windfall of hospital payment rates for E&M services for future acquisitions of physician practices that operate off the hospital campus. Yet the underlying dynamics

have not changed — the new policy does not apply to physician practice acquisitions that occurred before November 2015. Nor does the policy apply to drug administration or surgical services.

Certainly, physicians are complicit in the increasing integration with hospitals. The younger generation of doctors appears more focused on income security and balancing work-life commitments than the more entrepreneurial physicians of the baby boom generation. In a recent Jackson Healthcare survey, more than two-thirds of hospital-employed physicians reported they initiated discussions that led to employment. But physicians, like anyone, react to economic incentives inherent in the healthcare system.

One such incentive was the creation of Accountable Care Organizations (ACOs) by the Affordable Care Act. Physician practices — particularly specialists — felt under pressure to join ACOs for fear of being locked out of their markets and referrals. That program allowed 560 mostly hospital-led systems to receive bonus payments if they delivered care more efficiently than a predetermined benchmark. The thought was that this would encourage improved care coordination between hospitals and affiliated physicians and thereby lower costs.

Yet the vast majority of ACOs operated under one-sided risk, where they were not penalized if the cost of care exceeds the benchmark. Heads I win (with bonus payments); tails you lose (no penalty for excessive costs)!

Result: net losses of $216 million in 2015, according to CMS. CMS disclosed that 48 percent of Medicare ACOs produced no savings and 69 percent did not produce enough savings for bonuses in 2015. The $216 million loss is calculated by including total savings and costs, including bonuses to ACOs.

A few weeks ago, the MedPAC held a contentious meeting that failed to achieve consensus on whether Medicare payment policies should favor certain types of payment models (e.g., ACOs). Good! It should not be government's role to pick winners and losers.

Fortunately, the Medicare Access and CHIP Reauthorization Act (MACRA) created the opportunity for physicians to enter into different alternative payment models (APMs). MACRA's Physician-Focused Payment Model Technical Advisory Committee is presently evaluating physician-led APMs, with the goal of increasing CMS' present projection that only 70,000 to 120,000 (or 10 to 20 percent) of doctors will be paid through APMs. The committee recently endorsed two APMs for limited-scale testing, and HHS Secretary Price has called on physicians to submit new APM ideas.

But a key hurdle for better coordinated care and physician APMs is the "Stark" self-referral law, named after Pete Stark (D-CA), the longtime chairman of the Ways and Means Health Subcommittee. That statute, originally enacted nearly three decades ago, prohibits physician compensation for "value or volume," on the theory that physicians will order unnecessary items and services to maximize revenue.

Yet this antiquated statute does not permit physician practices operating in an at-risk or capitated APM to economically reward physicians that modify volume in order to abide by best practices. A coalition of more than 25 physician specialty organizations is now asking that the Stark law be modernized to allow the coordination and collaboration necessary for alternative payment models to succeed. Enactment of such reforms would not only improve care coordination, but allow for greater competition among specialty and integrated practices and hospitals.

And horizontal consolidation is no less concerning. Since 2010, there have been 561 hospital mergers, resulting in nearly half of all markets being anti-competitive. In 2015, mergers and acquisitions were up 70 percent compared to 2010. A Robert Wood Johnson Foundation study found when hospitals merge in already uncompetitive markets, the price increase often exceeds 20 percent.

Hospitals with fewer than four local competitors have prices that are nearly 16 percent higher than average — a difference of nearly $2,000.

In an April report, the Center for Health Policy at Brookings Institution said consolidation has led to a dearth of competition. That's why the healthcare industry sees rising prices, price variation, and uneven quality of care.

STEPS CONGRESS SHOULD TAKE TO ADDRESS THIS PROBLEM:

1. Reform the Stark self-referral laws to allow more coordination of care by physician practices and strengthen integrated practices as an important competitive counterweight to mega-hospital systems.
2. Reform 340B so that it benefits uninsured and indigent patients, not mega-hospital systems.
3. Build on site-of-service reforms, so that Medicare pays the same amount for the identical service regardless of where it is performed.
4. Provide more aggressive FTC enforcement of anti-competitive provider mergers and acquisitions.

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.

Noveome Biotherapeutics

To heal the wounds – maintaining and restoring cellular homeostasis with novel secretomes

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Noveome Biotherapeutics uses novel cell culturing to make therapeutic forms of "secretomes" to help heal wounds where the natural process of healing is impaired. Secretomes contain various cellular factors, normally produced by the body's cells, that use "paracrine signaling" to maintain cellular homeostasis and mediate immune responses. The company is in two Phase 2 clinical trials, one in treating allergic conjunctivitis in the eye, the other in treating gum and bone damage from periodontitis.

WHAT'S AT STAKE

Wound healing generates contrasting views, and even controversy, because wounds are so complex, involving an interplay of inflammation, nerve dysfunction, cell/tissue loss, and disruption to normal cell signaling and homeostasis. The complexity makes cause and effect difficult to discern; new treatments depend mainly on theory and empirical results, leaving a large void of unexplained mechanisms in between. Diagnosis and prognosis may overlook the tissue damage caused by comorbid conditions or focus on a single element entirely, such as bacterial infection. Once recognized, however, many intractable "wounds" associated with trauma or disease appear to respond to similar protein-based substances, Noveome's proprietary "secretomes," each one a novel collection of biomolecules with multiple targets associated with maintaining cellular health and genesis.

Noveome sees its lead product, the secretome coded ST266, as particularly suited to treating wounds of all kinds where healing is "impaired." Beginning with two discrete targets, in the eye and mouth, respectively, the company hopes to show the secretome's ability not only to heal damage by restoring cells, but also to prevent it by keeping cells in a healthy state, or "homeostasis." Secretomes work by addressing the local communication between tissue and cell via "panacrine signaling" — the short-distance analog to the long-distance endocrine signaling between cells in the body. "The one common theme is that whenever we place our product into a system where the paracrine signaling has been disrupted, either through continuous inflammation or removal of cells or bacterial contamination, the product is able to restore homeostasis and often function," says Clarke Atwell, president and CEO. The secretomes modulate inflammation as do steroids, but show none of the same side effects, he adds. "Our secretome also is able to accelerate impaired wound healing, and the important word there is 'impaired.' It has a neuro-protective property in the presence of inflammation as well as neuro-regenerative potential."

In recent research using ST266 in a preclinical model of optic neuritis, the secretome appeared to reduce inflammation and demyelination and rescue the retinal ganglion cells. "We think the mechanism for this may be related to mitochondrial biogenesis in those cells," Atwell says. "We were actually able to restore vision in the animal to close to baseline. We are currently working on a series of projects looking at other diseases in the back of the eye, in addition to our two clinical programs." One of the other promising effects of ST266 is reduction of vascular permeability, which could help block pro-inflammatory cytokines in the target location.

Noveome has gone through several reincarnations since it emerged from a complex of academic institutions around the University of Pittsburgh in 2000. Its initial plans to develop therapeutics from nonembryonic stem cells eventually put it on the path to creating unique cell populations with the ability to generate novel secretomes containing the desired molecules. Examination of the data the company has generated so far reveals good proof-of-concept, but only convincing results from larger trials in humans will open the door for this highly novel approach.

CLARKE ATWELL
President & CEO

Vital Statistics

45
Employees

Headquarters
Pittsburgh, PA

Finances

Total Raised
$19.1M
(Private Equity)

Non-Dilutive Funding
$114.4M
Since Inception

Last Private Round
$2.16M
In Venture
(April 2016)

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Latest Updates

January 2017:
Published preclinical data from a multiple sclerosis (MS) model study with ST266, the company's novel secretome and lead product, demonstrating its therapeutic potential for treating optic neuritis, the most common presenting sign of MS.

December 2016:
Initiated Phase 2 clinical trial of ST266 for allergic conjunctivitis. Data is expected in 2017.

June 2016:
Initiated Phase 2 clinical trial of ST266 for periodontitis. Data is expected in 2017.

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Last year BioMarin Pharmaceutical was ranked as one of the most innovative companies in the world. But longtime employees of the ultra-rare disease drug developer know that the company's future didn't always look so bright. In fact, when Jean-Jacques (J.J.) Bienaimé arrived in May 2005, things looked downright bleak. "A proxy fight had been organized by some of the shareholders who were trying to put in their own slate of directors," says the chairman and CEO. "The company had lost about $200 million the previous year, the stock (NASDAQ: BMRN) was trading in the $5 range, and employee turnover was around 25 percent." Many of his friends thought he had lost his mind when he took the job. After all, in the week prior, Bienaimé had finalized selling Genencor (a biotechnology company focused on industrial biotherapeutics) to Danisco for $1.2 billion. Following such success, why would anyone want to take charge of a "fixer-upper" like BioMarin? Bienaimé, though, was more optimistic. "I thought they had some good assets and people, and it just needed to be refocused and remanaged," he recalls.

BIOMARIN'S CEO – BAPTISM BY FIRE

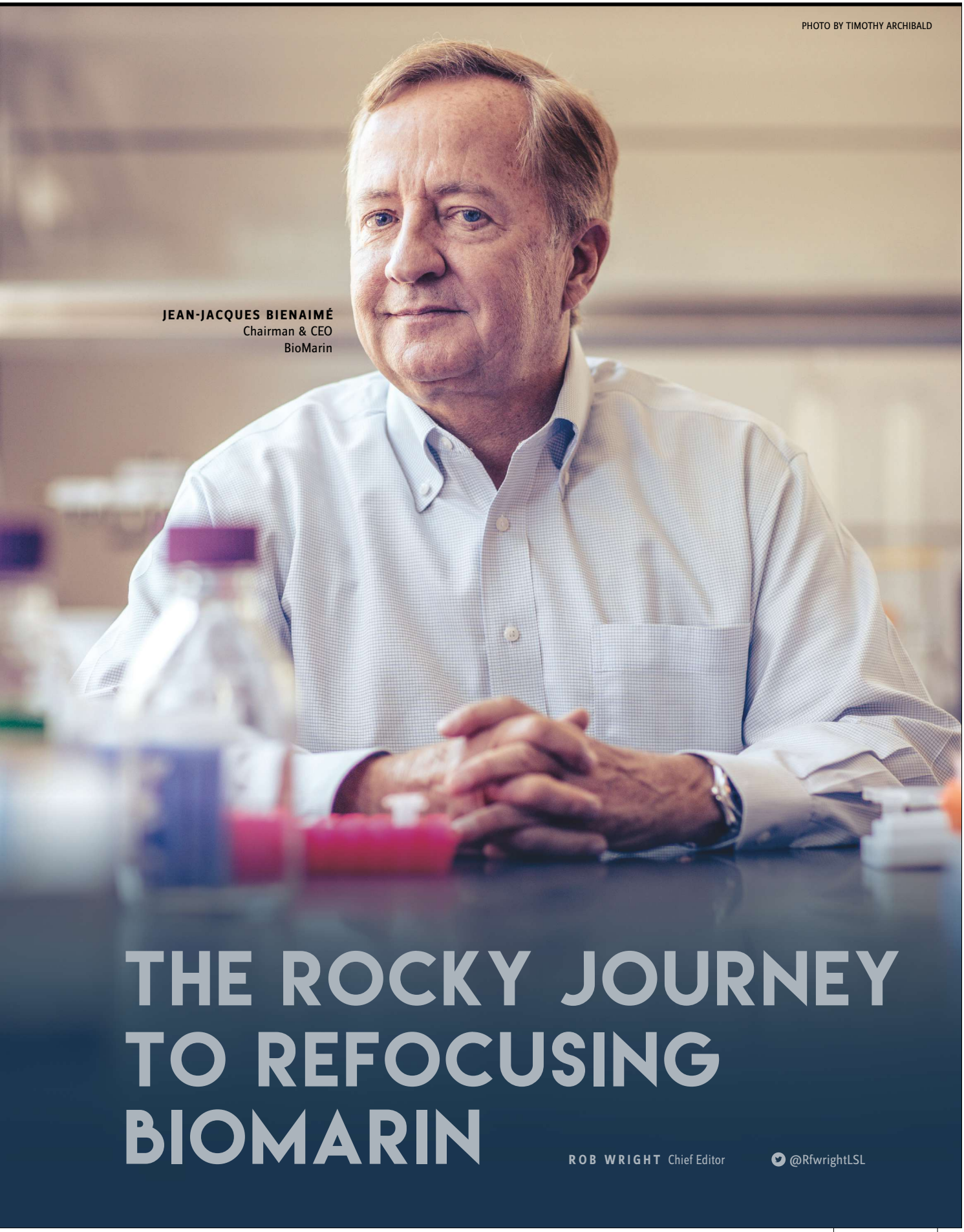
"I left Genencor on a Friday and started at BioMarin the following Monday," Bienaimé recalls. "I wasn't really planning on doing it that way, but there were a variety of things, such as the proxy fight and upcoming shareholder meeting, that had to be managed pretty quickly." The good news for Bienaimé was that the leader of the proxy fight was someone he had worked with previously — Sam Isaly, managing partner of OrbiMed Advisors. "I called Sam to figure out how to quickly get rid of the proxy fight and come to an agreement on board members," he shares. Over the next week, Bienaimé negotiated with the investor group, and on June 1, 2005, BioMarin announced a settlement with OrbiMed and its affiliated funds.

But as is often the case when dealing with a distressed business, there is usually more than one fire that needs to be put out. "The first day I joined the company I also had discussions with Serono," he states. Serono had been negotiating for ex-U.S. commercialization rights to BioMarin's phenylketonuria (PKU) franchise (i.e., Kuvan [an oral treatment], Pegvaliase [an injectable therapeutic], and any other future PKU products). Upon hearing that Bienaimé would be joining BioMarin as chairman and CEO, Serono gave him an ultimatum — sign the deal today or it's off the table. The agreement included an up-front payment of $25 million. At the time, BioMarin had about a month's worth of cash on hand, so Bienaimé felt he had little choice but to sign. "They were right to give an ultimatum," he admits. "Because had I been given a few weeks to think about it, I would not have done that deal." In addition to the deal providing a quick infusion of cash and potential future milestone payments (i.e., $232 million), it also offered a more immediate financial benefit. "Once mid-stage testing would be completed, Serono would share the development costs for the two programs, essentially cutting our drug-development costs in half," he explains.

With these two urgent matters now resolved, Bienaimé could now focus on restructuring and refocusing BioMarin. One of the first things he did was to ask his direct reports what they would do to fix the company if they were CEO. This exercise confirmed for Bienaimé that the leadership team was not only well attuned to the major issues facing the company, but had already considered ways to address those issues. He also bought his direct reports a copy of the book *Good to Great*. "I suggested they read it because my plan wasn't for BioMarin to be a company that just survives, but to truly evolve into something great."

The book lists one goal of great companies as getting "the right people on the bus, and the wrong people off." But there is more to it. Those "right people" need to be in their correct seats (i.e., in the proper positions to best move a company forward). "For instance, the person in charge of commercialization of future products was Emil Kakkis," Bienaimé relates. "But Emil had no commercialization experience, so I reshuffled clinical development and put him in a position where he could focus his drug development expertise." Other moves were also made. "You can't reorganize without a top management team," he attests. "But to truly become great requires a willingness to move people around, identifying areas where skills are lacking, and filling those expertise gaps."

PHOTO BY TIMOTHY ARCHIBALD



JEAN-JACQUES BIENAIMÉ
Chairman & CEO
BioMarin

THE ROCKY JOURNEY TO REFOCUSING BIOMARIN

ROB WRIGHT Chief Editor @RfwrightLSL

TOUGH TIMES: CUTTING EXPENSES ... AND PARTNERSHIPS

One of the other more pressing issues Bienaimé inherited when he took over BioMarin was a negotiation with Genzyme — a company partner since 1998 — regarding the ex-U.S. commercialization rights to Naglazyme (galsulfase) an enzyme replacement therapy for the treatment of mucopolysaccharidosis VI (MPS VI). "Though we were in desperate need of money, the reality was that Naglazyme was about 90 percent of the way to becoming an approvable drug," he says.

For about nine months prior to Bienaimé's arrival, a team at BioMarin had been putting together a term sheet for Naglazyme. But when the two companies sat down to hammer out a final agreement, it didn't feel like a win-win opportunity for BioMarin. "There were some advantages to letting Genzyme acquire the ex-U.S. rights to Naglazyme, as we had no employees outside the U.S.," he explains. "But the terms Genzyme was offering weren't that great, so it made the decision of telling them 'thanks, but no thanks,' a little easier." The decision to break off talks and keep the worldwide rights was a bold move by Bienaimé and BioMarin. "I had been here only a few months, and we were still somewhat shaky financially," he explains. "By not doing the deal with Genzyme we were making the decision to build a global commercial organization." In retrospect, Bienaimé says not only was the decision a correct one, but foundational to the company's current success. "Eighty five percent of Naglazyme's revenue comes from outside the U.S.," he explains. "If we had done the deal with Genzyme, it is highly likely that BioMarin would not be an independent company today."

In June 2005 BioMarin received FDA approval for Naglazyme. Later that month, the company launched the drug in the U.S., a rather difficult task when low on money and almost no revenue coming in. Key to that launch was creating a specialized sales force for Naglazyme, but with expenses already tight, the company couldn't afford to add staff. So, Bienaimé made the difficult decision to lay off the sales force (about 95 people) for Orapred, a corticosteroid that went generic only a few months after it had been acquired by BioMarin. That move saved the company about $9 million annually. "Layoffs are always tough, but for the launch of Naglazyme we needed salespeople with different skills from those selling Orapred, which was a very low-tech product," he explains. In addition, Bienaimé brought in Steve Aselage as SVP of global commercial operations. "He had worked for me at three companies prior, and I told him he needed to start building an organization to not only launch Naglazyme in the U.S., but Europe soon after."

The launch of Naglazyme in the U.S. was executed by a 10-member sales force; eight former Orapred reps that had been retained and two new hires. Though there would be additional staff added later, doing so required more cuts as well as fundraising. "Chris Starr was the head of research at the time, and he was in love with a technology that had been acquired by BioMarin that I

CHOOSING MARKETS FOR RARE DISEASE DRUGS

For BioMarin, the priority markets for its products are North America and the EU 5 (i.e., France, Germany, Italy, Spain, and the UK). "We also went to South America," explains Jean-Jacques (J.J.) Bienaimé, the company's chairman and CEO. "This decision was mainly driven by the geographic demand for Naglazyme." According to Bienaimé, mucopolysaccharidosis type VI (MPS VI) has a higher hereditary incidence in South America. "We started by first establishing a presence in Brazil, and then we went to other South American countries looking for patients. If we find just one patient in a country, it pays for us to put a country manager there."

He describes the country-to-country process as a very gradual approach that has led to the company doing business in other areas as well (e.g., Hong Kong, Japan, Russia, and Taiwan). Yet there are still some larger countries where the company is not selling its products (i.e., China and India). "It's an affordability issue, " he explains. "The products we have on the market today are very expensive. Though we are starting to sell Kuvan in China, and we have a couple of patients in India, neither of these countries has been a priority thus far." While intellectual property protection has been a major issue for why some biopharmaceutical companies have avoided entering China and India, Bienaimé sees this as a nonissue for BioMarin. "Our products are so complex to manufacture and difficult to copy that we aren't concerned with companies in these countries attempting to copy, at least not doing so successfully."

frankly didn't believe in," Bienaimé shares. "So I made the decision to give Starr the technology, along with a little money, and encouraged him to start his own company, which he did — Raptor Pharmaceuticals."

The Orapred sales force downsizing had a positive effect on BioMarin's stock price. But to further strengthen the company's financial position, Bienaimé took advantage of an existing shelf registration and raised nearly $60 million through the sale of 8.5 million shares of stock. BioMarin further added to its coffers by selling Naglazyme, which by the end of 2005 equated to $6.1 million, including sales outside the U.S. of $1.5 million. Things were definitely starting to look up.

With the cash crunch in the past and the company now generating money, it was time for the CEO to focus on what would drive BioMarin's future success — a pipeline filled with products.

BUILDING A PIPELINE

Beyond Naglazyme, BioMarin had only Kuvan and Pegvaliase in its pipeline, both of which it had sold Serono the ex-U.S. commercialization rights. So the company needed new products to fill its pipeline. "That's why we did a few small acquisitions," Bienaimé explains.

First, there was Huxley Pharmaceuticals (2009), which produced Firdapse (amifampridine) for the rare autoimmune disease Lambert Eaton Myasthenic Syndrome (LEMS). According to Bienaimé, this acquisition "helped keep our European organization busy and gave the sales force something else to have in their bag beyond Naglazyme." Then in 2010, BioMarin acquired LEAD Therapeutics, which added to its pipeline Talazoparib, a drug for the treatment of patients with rare, genetically defined cancers. After further developing Talazoparib, BioMarin sold it in 2015 (for a profit) to Medivation for $410 million.

The purchase of ZyStor Therapeutics gave BioMarin the proprietary Glycosylation independent lysosomal targeting technology. Though ZyStor's lead product (ZC-701) for Pompe's disease never panned out, the targeting technology has proven very valuable. "That is the technology we are currently using in the development of our BMN 250 product for Sanfilippo MPS III B Syndrome."

But the biggest acquisition — which could be described as an expensive lesson learned — was Prosena Holding NV. "In late 2014 we acquired Prosena for Kyndrisa [drisapersen], a drug in development for Duchenne muscular dystrophy," he says. "We learned a lot from that $680 million 'adventure.' Namely, we learned that it's very hard to overturn a negative Phase 3 clinical trial result with regulatory authorities." Though many view the purchase of Prosena as one of Bienaimé's biggest mistakes (i.e., Kyndrisa did not gain approval in either the U.S. or the EU), he remains optimistic. "We got a great R&D team based in the Netherlands," he reminds. "They are trying to develop a second- or third-generation molecule that is striving for a several-fold improvement in protein expression, and it looks like they might get there."

THE ADVANTAGES & CHALLENGES OF FOCUSING ON ULTRA-RARE DISEASES

Through these acquisitions, BioMarin strengthened its reputation as a developer of medicines for ultra-rare diseases. "Pursuing ultra-rare diseases allows us to move a little faster, because we are able to conduct very small trials," he explains. "We often execute Phase 1 and Phase 2 trials at the same time." For the recent Batten disease clinical trial, a pivotal study of 24 children taking cerliponase alfa (BMN 190), BioMarin did only one study — a combined trial of Phases 1, 2, and 3. "That's really the most aggressive a company can be," he attests. "By having a clear understanding of the biology of the disease, we avoid developing thousands of molecules just to see which one will 'stick to the wall.'" Instead, BioMarin attempts to design a molecule to address a disorder's fundamental problem. For example, though there are at least 20 genes associated with Batten disease, cerliponase alfa targets patients with a CLN2 mutation. BioMarin estimates there to be somewhere between 1,200 and 1,600 patients in the world with this particular mutation.

Though Bienaimé believes the FDA provides ultra-rare disease companies like BioMarin a little more flexibility when it comes to conducting smaller and simultaneous trials, he says it's still not easy. "You still need to have pure evidence of efficacy and safety to get your drug approved," he states. "We are always trying to be first-in-class or best-in-class, and we only go after diseases where there is a huge unmet medical need, where the biology is well understood, where there are existing biomarkers or where we believe we can develop the necessary biomarkers to guide early development, and where there is an existing natural history of the disorder." If the natural history isn't well documented for an area of interest for BioMarin, the company starts a registry. This is done to collect information and document how the disease progresses without treatment. In this

way, the company has data for comparison when it's able to execute a clinical trial.

BioMarin works closely with patient advocates to design trials that have meaningful endpoints. "This is never easy because regulatory and real-life endpoints often differ dramatically," he continues. "When you are striving to be first-in-class, there is no established regulatory pathway." As a result, BioMarin has to work collaboratively with regulatory authorities to help get these two sides (i.e., patients and regulatory) on the same "endpoint" page, as well as define a developmental pathway. "The gold standard for approval of a molecule by the FDA is two randomized, adequate, and well-controlled testing trials," he states. "We are far from this with our products." So far, BioMarin has only done one randomized testing trial for most of its drugs, the biggest being Vimizim (elosulfase alfa), which involved 176 patients with MPS IVA (also known as Morquio A syndrome). "We are always negotiating with the FDA as to what is needed to get an approval," he relates. "We try to help regulators understand the size of the patient population that is available for trials, along with ethical considerations when dealing with lethal or rapidly progressing disorders. Unfortunately, sometimes conducting a two-year randomized, double-blind, placebo-controlled trial simply isn't possible when working with ultra-rare diseases."

For Bienaimé, this focus on ultra-rare diseases was a big adjustment. He had come from a world where executing clinical trials involved thousands of patients to one where trials were much smaller and patients were enrolled quickly — which also meant BioMarin could go to market faster.

"I believe Big Pharma continues to struggle in the rare disease space," he says. "When you tell them they should be excited about a 3,000-patient global commercial market, they simply can't comprehend that." But there is a significant benefit to those companies that can do it successfully — lack of competition. Of the five products BioMarin presently markets, not one has any competition. Considering that BioMarin is operating in 60 countries with little or no competition, is it really any surprise that its stock is trading above $80 a share and its market cap has eclipsed $15 billion?

In 2014, CenterWatch reviewed 307 therapies approved between 2000 and 2013 and concluded that BioMarin was one of the fastest developers of medicines. One year later, EY named Bienaimé as entrepreneur of the year, and from 2014 to 2016 *Forbes* ranked BioMarin as a top 10 world's most-innovative company. That's a far cry from the fixer-upper he had taken the helm of 12 years ago.

GAINING PRIORITY REGULATORY REVIEWS

In January 2006, the U.S. FDA granted BioMarin a Fast Track designation for Phenoptin (sapropterin dihydrochloride), which is used to treat phenylketonuria, a birth defect that causes an amino acid to build up in the body. This was BioMarin's first product to receive such a designation. Since then, BioMarin has received numerous other priority regulatory reviews (e.g., Kuvan, Vimizim).

The latter was approved by the FDA in February 2015 for patients with MPS IVA (also known as Morquio A syndrome). But in addition to its drug getting approved, BioMarin also snagged a Rare Pediatric Disease Priority Review Voucher (PRV). The voucher allows its recipient to expedite the review of any one of its new drug products with the FDA by a period of six months. "We were the first ones to get a Pediatric Priority Review Voucher," explains BioMarin CEO Jean-Jacques (J.J.) Bienaimé. "But as we are mainly developing drugs that wouldn't have benefited by the use of this voucher, we decided to see if anyone was interested in buying it."

Before BioMarin started making a bunch of phone calls, the company first created a short list of all the companies with products either in advanced development or already under review at the FDA. "We wanted to narrow the process down to those who might be highly interested in saving six months of research/review time," he relates. One of the challenges faced by BioMarin was this was the first time a company had ever tried to sell a voucher. As such, there was no established market value as to what it could be worth.

The BioMarin business development team began making calls to see if anyone would be interested in purchasing a voucher. One of the companies the team contacted was Regeneron. "They were developing PCSK9 inhibitor, and were a little behind Amgen," Bienaimé recalls. "I remember I was mountain biking when I got a call from Regeneron's CEO, Leonard Schleifer. So I got off my bike, and we quickly came to agreeable terms." In retrospect, Bienaimé wonders if selling the voucher for $67.5 million was the right amount. Because the next voucher sold for $125 million, and the one after that went for $350 million! "But prior to us, nobody had done it," he reminds. "At the time, it seemed like a very good price."

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TAKEDA AIMS TO INVENT IT HERE & THERE

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Some companies seem to grow through sheer dynamism, absorbing and recreating their heritage as they go; others trace their roots back to the startup days and still measure their progress against their beginnings. Andrew Plump knows both environments, starting with his entry into the industry at the fabled Merck, then moving to the franchise-devouring Sanofi, and now leading a global overhaul of the R&D arm of Takeda, perhaps the world's oldest pharma enterprise.

GREATNESS & GROWTH

Plump came to Takeda only two years ago as a youthful but seasoned biopharma scientist and executive. (See the sidebar, "From Bench to Business.") He took on the position of Takeda's chief medical and scientific officer (CMSO), effectively head of global R&D with a strong hand in business development and partnering at the Tokyo-based company. Takeda's ancient origin in Japan belies its pioneering spirit, shown by its groundbreaking expeditions into the world's other major markets — most notably in the United States with TAP, an early joint venture with Abbott eventually to become part of Takeda, and later with more ambitious advances such as the purchase of Millennium in 2008. But for Plump, the company would be a big change from Sanofi, one of Big Pharma's youngest members. Fortunately, he says, Takeda offered an even more formative situation — one not just of growth, but of rebirth. Takeda and Sanofi also had something in common, a globalization-in-progress, that made the transition easier for him.

"There are so many wonderful facets to Japan: its history, its foundational value system, and its focus on good science," says Plump. "But I was a little bit concerned about going to a company whose center of gravity, so dense and strong, was outside of what I perceived as the core area of innovation in biomedical research, the United States. Yet I quickly realized the model Christophe Weber and chairman Yasuchika Hasegawa were building toward was an organization that had all the greatness of a Japanese company and all the potential of a multinational company." (See "Takeda's New Plans for Worldwide Growth," June 2016.)

Although the company was already committed to globalization when he arrived, Plump had the advantage of building from the ground up rather than struggling to change an already entrenched global organization. "Yasu had built up a very large global group, but it was immensely fragmented," he says. "When Takeda bought all those companies and essentially increased its size by two- to threefold, it didn't create any synergies; it didn't create any centralized structures. Its cost base became very high; it was very difficult to work in such an organization. Since I arrived, R&D has been going through a very significant organizational transformation to greatly simplify ourselves, reduce our footprint, and decrease our geographical dispersion."

Simplification has not only sped up internal communications, but also freed up resources for external collaboration, Plump explains. All but two of his direct reports now work with him in the Boston center, and the company's more limited focus on three therapeutic areas has streamlined operations — meaning

staff reductions mainly of people outside those areas: gastroenterology, oncology, and CNS, plus vaccines. He says the changes cut costs but in ways intended to concentrate resources strategically inside and outside. Just to organize into a centrally managed global group and collaborate with outsiders would bring an end to the traditional structure of Takeda. "We had to reduce our internal costs to free up capital so that we could actually do more externally, which required a cultural change along with the restructuring of our budget."

TURNING INSIDE OUT

It would be unlikely for such sweeping change to encounter no internal resistance in the 236-year-old company. Plump says he addressed the inevitable opposition with respect and calm explanation — "creating a very clear and highly rationalized, data-driven case for change." Personal visits and exchanges with staff throughout the organization, emphasizing the shared burden of change inside the company, reinforced the message.

In Plump's first days on the job, Weber worked with him closely to map out how they would communicate the "case for change" in the company. Weber also gave Plump a "gift," by ensuring the previous CMSO, Tachi Yamada, M.D., would stay on and work by his side for three months. Of course, eager to take on the job, Plump initially felt the gift might be constraining, but he soon came to appreciate its full value.

"Christophe said, 'Tachi's going to continue to lead your organization; you're just going to go and meet people and learn about the organization.' At first, I felt like I was in a straitjacket, but then I realized, this was a blessing, because it would free me to spend time understanding the group, and not just come in with my white-paper vision of what R&D should be. Instead, I could come to see what Takeda R&D should be. During that three months, I spent a lot of time learning and thinking before beginning to make changes. I first built my leadership team. Then we went out across the organization and we started talking about our case for change."

Plump says the "case for change" program was complex because the company is distributed over three major regions, all with different kinds of social and legal contracts. But the case revolved around an intent to focus on fewer therapeutic areas and a common set of statistics: In the previous 10 years, Takeda had brought 21 new drugs to market, but most of them were regional and only two were global launches. Only four came out of its internal labs, none of them global products. Ten came from acquisitions and seven came from licensing.

"In the future, it doesn't matter where our new products come from. The problem was with the way we had structured our budget — the vast majority of our money was going into our internal labs, yet the vast majority of our productivity was coming from our balance sheet." The case proved quite persuasive, according to Plump, and the employees could at least see how the organization could not continue as before.

"People might react to the message by saying, 'OK, the change you're making, I don't know if that's the right change, but I understand why you're making it.' We were even making major staff reductions in Japan, which is a place that's not used to that kind of thing, especially in the workforce. But every person understood the case for change."

EXTERNALIZATION – R&D MEANS BD

A restructuring of the R&D organization around the idea of increasing external collaboration on a global scale effectively puts Plump and his team on the front lines of business development. He now routinely seeks out, sets up, and oversees strategic partnering deals for Takeda. When executives say their first goal in every partnership deal is a "win-win" outcome, it can be tempting to dismiss it as a cliché. This is where meeting Andy Plump in person can redeem the phrase: He is as animated as a young child, but he is neither deceiver nor fool.

"People are surprised when you come to the table and say, 'Hey, what do you need to make this successful?' But if you create a deal that the partner will be upset about a year later, it will not be the right thing for the project, and nobody wins."

Plump says the company considers all of its R&D people as collaborators with the external partners. "Our group must have all of the technical competency and operational excellence necessary for doing external innovation — including financial transactions, venture and equity funding, alliance management, and so on." At his urging, the company established the new Center for External Innovation inside the R&D organization, led by Dan Curran, a physician-scientist with strong partnering skills.

Plump also led a shift in incentives from rewarding chiefly internal discovery and development to an equal emphasis on externally sourced programs. Another, built-in incentive, he says, is speed to market; external candidates generally enter the company's pipeline at the late-preclinical or clinical stages, perhaps saving up to five years in development.

"Wanting to do everything in-house is a tendency we all have as scientists because we love to create," he says. "But now we are starting to build a new culture where 'not-invented-here' no longer belongs. We're so excited about the opportunity to bring medicines to patients,

FROM BENCH TO BUSINESS

As a young adjunct professor and post-doc physician-scientist under the tutorship of Dr. Marc Tessier-Lavigne at UCSF, Andrew Plump was on his way to a predictable academic career. It was 2001, and he was 35 years old. Tessier-Lavigne was conducting basic neurology research in axon guidance, but it was difficult to see where the work would lead in medical practice, or how soon. Then a friend invited Plump to visit his workplace — at Merck & Co. The visit awakened something in Plump, a certain impatience with the pace of translation from basic academic science to new medicines that treat human disease. He fell in love with Merck and its R&D tradition and soon forewent plans to set up his own lab after completing his post-doc, jumping into the industry instead. "It was incredibly interesting, this idea that you could take science and translate it to therapies in the environment of a large pharmaceutical company," says Plump. "I found people at Merck who had backgrounds that were very similar to mine, who were driven, like me, and who were hyperfocused on this mission."

After starting in the translational medicine, clinical pharmacology group, Plump worked the next 10 years at Merck. At first, he missed the academic life and thought he'd made the biggest mistake of his life, but two stronger notions took effect: The realization that his dream of applying science was now at his fingertips, and the attraction of unlimited opportunity the company and the industry offered him. He remained at Merck and eventually served as head of the discovery cardiovascular group.

At that point, he was tempted by a job offer at the NIH with Francis Collins, a post promoted by his former mentor, Marc Tessier-Lavigne. Though he finally decided against taking the job, it had stirred the desire to seek greener pastures in his career. A week later, he got a call from the previous head of the NIH, Dr. Elias Zerhouni, who had just joined Sanofi as the head of R&D. Plump soon moved to Paris and worked there for Sanofi during the next two years. But, "almost too soon," he started to receive inquiries from Christophe Weber, the new CEO of Takeda. Plump resisted, but Weber was insistent, and after an "amazing conversation" by video conference between Paris and Tokyo, the resistance faded. Working at one of the industry's newest companies, Plump felt himself attracted to the long tradition and values of Takeda. A corporate disruption at Sanofi, resulting in the departure of Chairman Chris Viehbacher, came at just the right time to convince Plump to make his next career move, to the ancient Tokyo-based company. "Christophe mentioned to me that if I had not had the experience in a multinational company, I wouldn't have been the right person for the job. What I learned at Sanofi, in how to think about being in a truly global company not based in the United States, is a mindset that I now bring with me to the job every day."

to work on great science, that it doesn't matter whether the invention comes out of our labs or someone else's labs." He emphasizes that the company supplies not just monetary capital, but also intellectual capital to its partners, motivating the scientists on both sides to come together as peers.

Plump cites one recent example of the "intellectual capital" approach: Takeda's partnering deal with Ovid, a rare-CNS-disease company founded by the former CEO of Teva, Jeremy Levin (See October 2013.) The alliance involves a Takeda discovery, the compound coded TAK-935, a novel inhibitor of the enzyme cholesterol 24-hydroxylase (CH24H), which regulates cholesterol homeostasis in the brain. Takeda had done a number of dosing and disease-targeting studies before entering the agreement with Ovid to develop the drug in a rare pediatric epilepsy, now the target indication in a Phase 1b/2a trial.

The "risk-sharing" deal with Ovid stipulates the two companies will each bear 50 percent of development and commercial expenses for the drug and receive 50 percent of profits. Takeda will lead commercialization in Japan and other selected areas; Ovid, in the United States, Europe, Canada, and Israel. The deal also gives Takeda an undisclosed interest in its partner, likely in the midteen range.

"We're going to be close partners," says Plump. "As Ovid grows and grows, we might get more and more interested. We might start to partner with it on more programs, or to own more of the company. But if it's not successful, we'll move in a new direction. That's the agility we're looking for in our externalization. It is also an example of how we are using one of our molecules to gain access to Ovid's expertise without building it all inside. If we built all of that inside and ultimately the program died, we would be left with this large infrastructure and all these great people, and what do they do? Instead, we try to find great science outside and to partner with that great science."

ACADEMIC SOURCING

An even more primary source of outside innovation is academia. Locating Takeda R&D in Boston is no accident. Biopharma startups now contribute most of the industry's innovative products, and academia is the source of most biopharma startups and products. In the United States, where the majority of biopharmas originate, San Francisco and Boston account for 70 percent of those companies. And Boston seems to be clos-

ing fast on its West Coast rival for the title of industry's leading urban center. Key to the attraction of both areas is the same, however: the presence of powerhouse universities producing world-leading life sciences. When Takeda bought Millennium, it was undoubtedly for its oncology programs, but now the Boston location has global significance for the company's entire R&D organization, strategy, and results.

Still, Plump maintains the company has sufficient presence elsewhere to tap good science as it emerges around the world. It also has a new model in the works for helping academics do drug discovery that would translate more directly into therapeutic compounds. "There are platform technologies such as small molecule chemistry or antibody production that are reasonably scalable. We can do them; almost anybody can do them. Individual-target drug discovery on those platforms can come straight out of academia. It doesn't need biotech, venture capital, or even pharma, but it does need infrastructure and some capital to support it. We will take our expertise and support directly to academia to help implement such a drug-discovery model."

When Plump joined the company, it had already started an "experiment" in translating academic science into commercial programs. In New York City, Takeda entered a partnership with Weill Cornell Medical School, Memorial Sloan Kettering, and Rockefeller University — the Tri-Institutional Therapeutic Drug Institute (Tri-I TDI). Under the leadership of scientist/entrepreneur Michael Foley, the institute directs a lab staffed by 15 Takeda chemists, who produce and test molecules matching individual targets identified by academic scientists and cleared by an independent scientific advisory board. Any compounds that show commercial promise then pass to a funding entity, Bridge Medicines, a construct of Takeda and two VC firms, Deerfield and Bay City Capital. Bridge supports further human testing through proof of concept.

"The cost structure in this model is a fraction of what we would pay internally," says Plump. "Although it's only an experiment, it's a really interesting experiment. Marc Tessier-Lavigne, formerly at Rockefeller and now at Stanford, is helping us build a similar program there. We're also looking in Seattle, and obviously in Japan. I'd love to put together a half dozen or more of these programs to equal a fifth to a quarter of our internal discovery organization, in this direct interface with academia." He says a key aspect of the program is Takeda does not own it — the model can evolve in this entrepreneurial setting without the company controlling it. "But we have first-negotiation rights to the results."

Another example is T-CiRA (Takeda-Center for Inducible Pluripotent Stem Cell Research and Application), a translational regenerative medicine institute located within Takeda's research center in Shonan, Japan, and run by Nobel Laureate, Shinya Yamanaka. T-CiRA houses approximately 100 scientists, led by principal investigators primarily from Dr. Yamanaka's host institution, Kyoto University, home of CiRA. Takeda and Yamanaka are in year two of a 10-year partnership to develop therapies based on the iPSC technology.

MANUFACTURING INNOVATION

As our Outsourced Pharma chief editor, Louis Garguilo, often reminds us, biopharma innovation begins with, and often happens entirely within, manufacturing. Of course, industry insiders know manufacturing is about much more than churning out finished units. With proper planning and design, innovation can occur at any one of its many stages, from compounding and formulation through quality testing, and probably on to even more finely defined activities. Manufacturing, in its broadest sense, is also one of the primary capabilities a large company like Takeda can offer its partners. Also important, the larger company is more likely than the typical startup to realize manufacturing must begin as early as possible in the life of a new drug.

"If you're not thinking about manufacturability and formulation early on in your discovery program, you'll make decisions that prove to be irreversible mistakes," Plump says. "And if you wish to employ some of the new modalities emerging, you must address the issues around them. With cell-based therapies, modified T cells, gene therapy, biologics — if you're not immediately thinking about manufacturing, forget it, because you will likely face cost of goods or supply chain issues. This is a huge part of what we do."

Plump describes how Takeda's pharmaceutical sciences group aligns discovery and development with the manufacturing group to smooth the transition from one to the other, mainly through early planning. Although compounds with advanced modalities need the earliest possible attention, even the common small molecule drug can present unexpected vagaries, as well as opportunities.

"With a small molecule therapeutic, as you go through optimization, if you just think about how to optimize potency to the target, and not about all the other properties that are necessary, you'll make bad, irreversible decisions. It is absolutely critical to have pharmaceutical scientists with deep technical expertise around formulation, process chemistry, and other fundamentals involved early on in the lead-optimization program. We co-localize these scientists. They work together, and as they choose which molecules and which paths to take on to optimization, they're thinking in a multi-faceted way."

MEASURES OF PROGRESS

Whether Takeda's "invented here and there" approach to R&D works out well in practice will hinge on the quality and performance of the pipeline it builds along with the new organization. For now, the company can measure success by the milestones it sets for itself in what Plump calls a three- to five-year process, now only in its second year. One of the key posts in Takeda R&D's progress is how effectively it can attract high-quality partnerships and assets. The quantity is important for two reasons: first, the promise of the innovation the partners present; second, the show of confidence in Takeda suggested by the eagerness and satisfaction of the deal participants.

By those measures, which Plump clarifies as not metric- but qualitatively driven, the external drive in R&D has proceeded well. "In the past 18 months, we've put one acquisition and 50 partnerships in place," he says. The selection of deal targets follows some simple criteria. Each target must: fit in one of Takeda's three therapeutic areas; meet a high innovation standard (high unmet need; cure over incremental therapy); and, of course, have the potential of being an excellent partner.

The acquisition Plump mentions is of Ariad, completed in February of this year. Ariad brings additional hematology and oncology products into Takeda's pipeline, and one product into its commercial portfolio: Iclusig (ponatinib), approved for treating leukemia.

"When we started to look at Ariad, we thought right away, this is a perfect fit for us strategically and culturally, and then they saw it as well. We told them we didn't want to get into a bidding war and proposed we do an exclusive negotiation to complete the deal in two weeks. We put in a price that was very competitive, purposely. Ariad agreed to the exclusivity because we're focused — we don't have a billion things going on in a thousand therapeutic areas. After the essential due diligence, we came out with a great acquisition and really innovative products."

With such a large project to run, Plump sometimes encounters issues that can keep him awake at night, but his overall excitement about the job gets him up every morning, eager and ready. He is still inspired by his original motive for joining the industry, turning cutting-edge science into new and better medicines. At times, he says, he hardly believes he can have so much fun — and still get paid for doing it.

ROB WRIGHT Chief Editor @RfwrightLSL

JOURNEY TO THE CORPORATE BOARDROOM

PART 3: CURIOUS WHAT SERVING ON A CORPORATE BOARD ENTAILS?

If you have never served on a corporate board, you might be curious as to what it all entails. Thanks to BioBreak and Drexel University, *Life Science Leader* undertook the development of a three-part series of articles titled "Journey To The Corporate Boardroom." Part 1 explored how to seek a board opportunity, while Part 2 dug into what leaders should be thinking about when building their company boards. In this final installment, we delve into what serving on a corporate board is really like. For insights we engaged the following five executives: Richard Baron, former CFO and board member of Zynerba Pharmaceuticals; Rich Daly, president, CEO, and chairman of the board for Neuralstem; Don Hayden, former global pharmaceuticals president for Bristol-Myers Squibb and current board member of several biopharmaceutical companies; Kirk Gorman, former CFO and EVP of Jefferson Health Systems and board member of several companies; and Gwen Melincoff, founder of Gemini Advisors and board member for Kamada Pharmaceuticals and former board member of Tobira Therapeutics.

LIFE SCIENCE LEADER (LSL): Walk us through your recent board service experience while also managing expectations at a current employer.

GWEN MELINCOFF: I joined the Tobira Therapeutics board when I was in between positions at Shire and BTG. In fact, one of my conditions when accepting the position at BTG was to remain on Tobira's board. Having served on as many as six boards at one time when employed by a public company (i.e., Shire), I thought I had a good understanding of my priorities and felt I'd be fine. As it turned out, it did require an inordinate amount of time. I had a manager in London who didn't really know what I was doing other than four times a year I would go out to California (a two-day trip) to do some board work, not to mention the numerous monthly phone calls as part of my serving on various board committees (e.g., the compensation committee). Despite my board service being a larger commitment than anticipated, my employer remained very supportive. And though I had previously served

on a number of boards at the same time, I am not sure I could have handled serving on more than one in this instance, as Tobira went through two transactions that involved a significant amount of board work (i.e., an IPO and a $1.7 billion acquisition by Allergan).

LSL: When you joined Neuralstem as the CEO, the former CEO was still on the company's board. How do you manage running a business and serving on the board with a potential "backseat driver"?

RICH DALY: For starters, you have to be pretty up front about who's in charge. I remember talking with the board when we first met and I asked, "Who's in charge?" They responded that I was. So we were very clear from the beginning on who was accountable for the day-to-day running of the business, while the board would be involved in higher-level decision making. That being said, having the ex-CEO on the board or having access to the ex-CEO can be very valuable. There are a lot things that happen in the day-to-day running of the business that the board is not involved in, which is a good thing, because that is not their role. And though the ex-CEO wasn't running the business, I could call him when I had questions. For example, I recall looking at some documents and determining that something appeared to be missing. So I called the ex-CEO and he told me where to look for the needed information. If you are the CEO and find yourself in a similar situation, set the operational guidelines for that relationship very early, and very firmly, as this will be critical to your success in working together.

LSL: What has been your experience regarding the time commitment required for serving on a board?

KIRK GORMAN: To be an effective board member requires a fair commitment of time and energy, such as outside boardroom reading and thinking and interacting with management and other key stakeholders. I think many people underestimate the level of commitment required beyond routine board meetings. My advice would be to think carefully about how much time you have to commit. How much flexibility do you have to adjust other parts of your life to what board and committee meetings may require, because the scheduling of these meetings is not completely under your control and you are expected to be there.

Serving on boards will provide for conflicts and pressures, and that's normal. But one of the positives of serving on a board is it gives you access to different ways of thinking and exposes you to different approaches to tackling similar problems. Even if the industry is a little bit different from the company you work for during the day, the running of a company has a lot of similar themes, and seeing how other executives and board members approach those same challenges and issues can be very helpful to your day-to-day job. One of the reasons I was permitted to join a couple of boards by each of my employers was because the leadership thought it was useful to have me learn how other people approach similar problems and how to identify opportunities for improvement.

LSL: What about serving on a board that has a dysfunctional management team?

RICH DALY: If you are on a board, you have to keep in mind that you are not a manager but a steward of the organization. When serving on the board of a company other than your own, keep in mind that you are diving into the company four times a year officially, and depending upon company specific circumstance, maybe a few other times as well. So a board member might be getting little pieces of information, which can make it very difficult to understand what the real issues are let alone determining perceived management dysfunction. Serving on a board versus managing is shockingly different and an unbelievable exercise in patience. When in management and serving on a board, you have to work with the board and move very carefully as you are getting inputs from all over. However, if you are seeking to serve on a board for which you are not also serving in management, it pays to be thoughtful in how you approach challenging management. When you think about the fact that the average board takes about 250 to 350 hours a year, to truly understand a dysfunctional situation requires a much bigger investment of time.

DON HAYDEN: I'd like to add to that. Depending on where the dysfunction is, the answer may differ. If the dysfunction is the CEO, then the board has to be far more active in addressing it, because the CEO is the board's responsibility. If the dysfunction is elsewhere (e.g., CMO, CSO), and you're happy with the work the CEO is doing, then that is more of a situation where the board will work in partnership with the CEO to try to understand and help develop a plan for how to address it. On one of the first boards I served, at the request of investor directors, I was asked as board chairman to evaluate the CEO and recommend a plan of action to the board. This was because the investors were concerned about the "disruptive effect" the CEO was having on the company.

IN THIS ARTICLE

RICHARD BARON is the former CFO and board member at Zynerba Pharmaceuticals.

RICH DALY is president, CEO, and chairman of the board for Neuralstem.

DON HAYDEN is the former global pharmaceuticals president for Bristol-Myers Squibb and current board member of several biopharmaceutical companies.

KIRK GORMAN is the former CFO and EVP of Jefferson Health Systems.

GWEN MELINCOFF is the founder of Gemini Advisors, board member for Kamada Pharmaceuticals, and former board member of Tobira Therapeutics.

LSL: What about the trend of corporate boards shifting their focus from governance to company strategy?

DON HAYDEN: This is a natural occurrence as boards move away from a "check the box" mentality of governance toward a more dynamic and forward-looking dialogue. This usually happens when the question "what if" begins to be posed. For example, what if we succeed? What if this works? What if this happens? What if this doesn't succeed? Further, boards are becoming more focused on evolving and developing themselves. For example, take the question of mandatory retirement age or board tenure limitations. In my opinion, the best boards are moving away from these things as they seek to assess and address board capabilities and demographics (e.g., diversity) on a more continuous basis. In fact, over the last five years on both private and public company boards, I've had discussions with individual directors about how they can add greater value to the board going forward, or in some instances, how they might best serve the board by transitioning off. Such discussions around board experiences and competencies no longer lining up with where a company is going is a direct result of the dynamic work boards are doing around company strategy.

LSL: What can you share about serving on a board of a company while it is being acquired?

GWEN MELINCOFF: Deciding on if a company wants to be acquired or not is the responsibility of the board. Once this has been determined, the board then has to go through a process of determining fair value, making sure it has the right economics for the company, hires the right advisors, the right bankers, and so on. When I was in Big Pharma, we typically did not use banks to do our deals, but when you are a small public company a lot of times you tend to use a bank to help execute the deal. When Tobira was being acquired by Allergan, we had an auction (i.e., a business sale process where a group of buyers make their final and best bids and the company going to the best bid), which was very intense. In such a situation, the banker may tell you there is someone else in the auction mix, but you never know for sure. In my experience, time feels much more compressed when serving on a board during an acquisition. From start to finish, the Allergan-Tobira deal was done in approximately two months. But each deal, depending on if you are on the buy side or the sell side, is different and can come with its own distinctive pressures.

LSL: What is one tip you'd offer to those considering/serving on corporate boards?

RICHARD BARON: Participate on boards like it is your job. You are a representative of the company, and as such you need to apply the same ethics and everything else associated with being an employee because it is your and the company's reputations at stake.

RICH DALY: Above all, know yourself. Are you a builder or a first responder? My passion is helping companies overcome big challenges — transitioning from clinical to commercial, turnarounds, etc. Thus, I'm a first responder and energized by having an opportunity where I can make a huge difference. If you're the type of person who is most comfortable with more than 12 months of cash on the balance sheet, then these kinds of opportunities are likely not for you.

GWEN MELINCOFF: You're judged by the company you keep. It is really important when you join a board that you know who those board members are, what you can contribute to the company, and what they can give you.

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WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Part 2:
Leading Business With Science
Geert Cauwenbergh of RXi

In part two of this article (see April's issue), we continue the story of Geert Cauwenbergh whose nearly 40 years in the industry included work with Paul Janssen as well as being a startup entrepreneur with RXi Pharmaceuticals.

OUT ON HIS OWN

It seems even the simulation of entrepreneurism in a corporate environment could not satisfy Cauwenbergh's own enterprising spirit — an inheritance from his years at Janssen. Yet yearning for change is never enough, either; to affect the world, an idea must take physical form. Once again, his natural gregariousness led him to a fateful meeting of minds.

"I had gotten to know Seth Harrison, who headed Appletree Ventures, then a small venture fund, and our wives also became friends, because they are both painters. We liked to hang out at the Markt, a Belgian bar and restaurant in Manhattan, where Seth and I would talk about the business, and our wives would talk about art. One day, Seth suggested I take some of the money from the generous compensation J&J had given me and start my own company, rather than spinning companies off and letting other people run them. When my wife and

I got home that evening, I told her I wanted to follow Seth's suggestion, and she agreed, because she knew I was unhappy with the status quo."

He spoke with J&J management and won an agreement to back his startup. "I said, 'Can I take all of your prescription derm assets in development, including the IP, and spin it out in a company?'" Chairman Weldon approved and stipulated the terms of the deal: no commercial assets, only R&D assets; the company must raise a minimum of $35 million from investors. J&J would take $25 million in equity in the company but no cash payments. Unlike the other spinoffs, the new company would market any products it successfully developed. "Six months later, we had raised $46 million, not $35 million, and initially we kept the company private."

The startup was Barrier Therapeutics, and in April 2004, the company took a then unusual step for a spinoff of going public, raising another $75 million. Barrier drew more than products from J&J, says Cauwenbergh. "I had a fabulous team. J&J was also nice in letting me pick and choose whom I wanted from their employees. They would say no, if they really didn't want the employee to go. But we had a little fight over only one person, but in the end, they realized that one person was not happy and would've been happy with me, and they allowed him to go as well."

Barrier started with a few small but close-to-market products, getting them all approved in only three years and on the market in 2006. By 2008, when Barrier was acquired by Stiefel Labs, the company's revenue had grown from zero to $45 million. By the acquisition terms, Cauwenbergh had to observe a noncompete clause for 18 months, during which he tried some vacationing and consulting. He finally jumped into a bigger assignment as a consultant running a small, regional drug licensing and development company, RHEI Pharmaceuticals. RHEI was active in China, and he commuted there frequently, literally expanding his horizons as a CEO. Ultimately, he sold RHEI to a local, midsize Chinese company, a difficult feat following close on the meltdowns at Stearns and Lehman Brothers.

ON TO THE PRESENT

By mid-2010, Cauwenbergh was free of RHEI, but he stayed busy serving on several bio company boards in Belgium, Canada, and the United States, until November 2012, when he answered a call from Kevin Tang of Tang Capital in San Diego: "Geert, we know you have a lot of experience in dermatology and wound healing, and you've taken companies public. We are looking for candidates to become the CEO of a spin-out from CytRx."

In 2006, CytRx, an oncology company, spun off an RNAi (RNA interference) company started by Nobel Laureate Craig Mello and colleagues. The spinoff was initially called RXi, but later named Galena when it acquired Apthera, a developer of therapeutic vaccines. By Cauwenbergh's account, RXi had previously raised money, but then went through a shareholder tussle over whether it should use the funds for the Apthera purchase or spin out the RNAi part of the company and declare a dividend. In the end, it did both, buying Apthera and spinning out the RNAi programs into yet another company bearing the RXi name. With more than a thousand shareholders at the time, the new, tiny RXi had to go public immediately.

Cauwenbergh heard from Tang when the spinoff deal was still in progress, with personnel and contractual issues still pending. "I told Kevin Tang, 'You don't want me as the CEO at this point. A consultancy should be fine. If you give me a CEO contract, and the spinoff deal falls through, you'll have to pay me one year's severance, and I will hold you to that.' Kevin said, 'Consulting is fine.'"

The consultant arrangement also worked better for Cauwenbergh, because it gave him time to do a deep dive into the RNAi space and the science behind RXi's platform. All he knew then was the space had an abysmal record of failure.

But the week before Tang had to sign the spinoff deal, he called Cauwenbergh, wanting an answer to the CEO job offer. "I asked Kevin what he planned to do if I didn't stay to take the job. He said, 'You've seen a lot more than I have seen. If you're not doing it, it means there's something fishy that I missed, so I'm not going to put my money on it.' I told him 'that would be a major mistake. I think this is potentially a gold mine.' A week later, Kevin had invested, and I came into RXi as the CEO of the company."

STILL ACTIVE AFTER ALL

It has now been five years since Cauwenbergh took the helm of the early but ambitious RXi. As with the other major steps in his professional life, it brings significant changes in scale and risk. RXi's technology, development goals, and drug candidates are not licensed assets. They all arise from the company's own research.

RXi started with strong science, giving it confidence its novel approach would greatly improve the effectiveness of RNA interference. Many previous approaches relied on delivering the RNAi agent in a lipid-based medium, which helps the RNAi agent penetrate the cell as a foreign substance. RXi's technology, called self-delivering RNAi compounds (sd-rxRNA), uses no delivery vehicle; the sd-rxRNA enters the cell and "loads" directly into the RNA-induced silencing complex (RISC). RISC is a cellular constituent in the normal pathway for silencing messenger RNA. In the case of a therapeutic RNAi, this silencing mechanism is exploited to reduce

the production of disease-causing proteins. Thus, the sd-rxRNA agent acts as the active drug with improved cellular uptake, free of a delivery vehicle, for local application not restricted to certain tissues.

For the same reasons Cauwenbergh had hesitated before joining RXi, raising money in the RNAi space was anything but easy. For the first year, his job consisted mainly of securing more funding. "Fortunately, we had another senior person in the RNAi space, Dr. Pamela Pavco, chief development officer. She's highly regarded and capable of running the company internally while I chased new money, because to start we had only enough money for perhaps a year, maximum."

In January 2013, he saw Phil Frost, an investor he had known since his time with Janssen Dermatology. "Phil said, 'Geert, RNAi drugs, they don't work. I spent $35 million on a Phase 3 program for one, and it failed.' But Dr. Pavco was with me, and she showed Phil the data from our preclinical studies, along with the fluorescence images of how our drug got into the tissue and the old conventional sRNAs did not get in. Phil looked at me and said, 'Geert, we may do a deal this time.'"

Frost soon agreed to lead a deal worth $16.4 million, with no discounts or warrants, and RXi's share price rocketed from $64 to $100, which in hindsight, says Cauwenbergh, seemed a bit "exaggerated." But he had no reason from his prior experience to justify questioning the company's apparent good fortune — until luck took a mysterious downturn. "Every time we issued a press release, the volume would go up, but we went down. Volume and price would rise in the morning, and then in the afternoon, the price would fall 5 to 10 percent lower than when we started — with good news!"

Time for a lesson in the financial business: "I thought something must be wrong here, and it turned out, whenever we issued a press release, Kevin Tang would basically short-sell and then send a conversion letter. That started in January 2014, and when he was done selling in May 2015, our common shares outstanding had gone from 12 million to 41 million, and our share price from $64 down to $4. Then we really had to raise money, this time in a market without warmth. That's when I lost my virginity in that space — because it was the first time I did a deal where I had to give discounts and warrants."

MULTIPLICATION BY ADDITION

And it would not be the last time. In late 2016, Cauwenbergh needed further funding to finance the purchase of MirImmune, a company that significantly multiplied RXi's development options. RXi issued an $11.5 million underwritten public offering of securities, giving underwriters an option to purchase additional shares and warrants.

"I don't like this dilutive cycle of financing, and I want to try to find a way to break out of it, to be able to create value for my long-term shareholders," he says. "The MirImmune deal may actually become a significant way to achieve that goal."

MirImmune, an immuno-oncology developer, had previously licensed and conducted valuable research on RXi's technology. MirImmune had its own development programs using the sd-rxRNA platform, including anti-PD-1 and other IO compounds. Essentially, the program may offer a gene-silencing alternative to conventional CAR-T or mAbs for inhibiting tumor checkpoints. By the time of the acquisition, MirImmune's research had identified at least one compound each for six different checkpoints and had developed ways to load up to four different checkpoint blockers in the same cells — combination immunotherapy in a single cell-therapy agent. One of MirImmune's programs also aims at cosimulation of tumor-infiltrating lymphocytes (TILs).

The original licensing deal between RXi and MirImmune came at a time both companies were low on cash, so they had to improvise. RXi accepted a 10 percent equity in the other company in a warrant with five years of dilution protection. With the license, MirImmune garnered about $0.5 million from one its founders, Timothy Barberich, as well as some NIH funding. When it returned to RXi with the results of its testing, both companies decided it was a good time to merge. RXi now has programs in dermatology and ophthalmology in clinical, and immuno-oncology in preclinical development, aiming to start its first trial in immuno-oncology in 2018.

ALWAYS LOOK BACK

One way to envision Cauwenbergh's career is that it has come full circle — returning to the entrepreneurial, ground-breaking environment that gave Janssen its cutting edge. His story is one of beginnings, not endings, of learning new things every day and seeing newborn possibilities and challenges at every turn. But it is also a tale of applying knowledge and experience,

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Out Of The Congo — Janssen's Therapeutic Legacy

It is difficult to superimpose the history of Janssen on the history of the Congo, also known as Zaire, although the fate of the company and the Congo's separation from Belgium closely coincide. Only the few key facts remain. The colony, Belgian Congo, became independent in 1960. By 1961, when J&J acquired Janssen, the company was still young but fated to become a global player and record-breaking originator of new medicines meeting long-unmet needs. Its success would rely in great part on medical researchers who had worked for the Belgian government in the Congo's universities and returned to Belgium when their jobs ended with the colony's independence. Some of them had been exploring new therapeutic avenues for diseases especially common in the tropics, though actually present nearly everywhere, such as fungal infections and diarrhea. Paul Janssen selected several of the ex-colonial scientists to build and expand his R&D organization in Belgium. By the end of the 1960s, the Janssen company had developed some of the first effective medicines for fungal infections, parasites, and GI disorders, reflecting its interests and roots in the Congo. It maintained a long-term connection to the former colony, keeping a small commercial operation in the country. Paul Janssen visited the area multiple times, and the company later funded AIDS-related clinical research there, staying one step ahead of the worst upheavals, until total war forced an end. At that point, the last Janssen-funded researcher finally left Africa, albeit reluctantly. Returning to Belgium and joining the company in 1992, Dr. Paul Stoffels, now the cochairman of J&J's combined Janssen pharma business, would subsequently build on his scientific and clinical work in Africa to champion a generation of breakthrough anti-HIV medicines.

based on an understanding of industry history and scientific progress.

"If you go time and again through the same system of developing new drugs and you don't learn from the failures that people have made, you will make the same failures, possibly costing lives not only as result of toxicity and side effects, but also because you waste time in getting life-saving medicines to the market. Think about where we were as an industry in 1900, 1950, 2000, and where we are today. It has been an exponential, evolutionary growth of knowledge. You need to learn about its history; otherwise, you will have to retrace the learning curve."

One general lesson from the industry's history: Its most-effective leaders have succeeded by maintaining a creative balance of science and business. In Cauwenbergh's case, the ability to blend those two disciplines proved to be an advantage in every job he had — starting with Janssen and its phenomenal founder.

"Paul Janssen always said that I belonged in R&D, and if you have that in you, the business piece you can learn — and even if you don't know all of the technicalities of R&D, you can learn how to grasp an essential understanding of the science. I was of very practical use to Dr. Paul. I could explain relatively complex matters in such a way that an average general practitioner or a nurse practitioner could understand what we were doing. And I could write about it; I published a lot. That is probably why he liked me, and I know that is why he took me under his wing, because he told me that."

Cauwenbergh has one more piece of advice for new industry explorers: Always have an open, prepared mind. "Be prepared to accept the unexpected, and recognize it as an opportunity, because that is when greatness is born." Words of wisdom from someone who is not only a fascinating storyteller, but also a careful listener. L

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Funding For Biopharmas
Targeting Urgent Bacterial Threats

CATHY YARBROUGH Contributing Editor @Sciencematter

A Nevada woman's death in 2016 from an untreatable bacterial infection called attention to the possibility of an "antibiotic apocalypse," when even the most deadly bacterial strains will prove resistant to all available antibiotics. "Antibiotic development is not keeping pace with the emergence of antibiotic-resistant bacterial strains," said Kevin Outterson, executive director of the new global public-private partnership, Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). Headquartered at Boston University (BU), CARB-X was launched in August 2016 to accelerate the preclinical development of innovative, high-quality antibacterial products at biotech startups.

New antibiotic classes are far too rare, said Outterson, BU professor of law and a global thought leader on the economics of antibiotic development. *(Editor's note: See adjacent article on newly proposed economic models for antibiotic R&D.)*

On March 30, CARB-X awarded its first round of grants to about a dozen biotech startups with highly promising therapeutic, preventative, and diagnostic products that target microbes on the CDC's 2013 list of urgent and serious bacterial threats. The grants will be heavily weighted toward Gram-negative bacteria, which include CRE, the microbe that killed the Nevada woman. CARB-X's funding portfolio is not limited to antibiotics, because vaccines and rapid point-of-care diagnostic tests also will help protect the public from resistant bacterial strains, said Outterson.

CARB-X was established in response to the U.S. government's National Action Plan for Combating Antibiotic Resistant Bacteria. Funding CARB-X's five-year budget of $350 million are the U.S. government's Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Disease (NIAID), as well as the U.K.'s Wellcome Trust and AMR (Antimicrobial Resistance) Center.

While CARB-X will not finance Phase 2 or 3 clinical trials, the products that emerge from the startups supported by the organization's grants will be in a position to attract the public or private investment required to finance costly late-stage clinical evaluations.

> *"The science is definitely out there, but it has been starving for funding because private money is not being invested in the preclinical space for antibiotics."*
>
> **KEVIN OUTTERSON**
> Executive Director, CARB-X

"A lot of interesting science is occurring at small biotech companies," Outterson said. "The science is definitely out there, but it has been starving for funding because private money is not being invested in the pre-

NEWLY PROPOSED ECONOMIC MODELS FOR ANTIBIOTIC R&D

Efforts are underway in the U.S., the U.K., and Europe to create new economic models for antibiotics that will encourage more biopharmaceutical companies to invest in the preclinical and clinical development of these essential drugs. (The last new class of antibiotics was developed 40 years ago.) While primarily focused on antibiotics, the groups that have been leading these efforts also have emphasized that high-quality vaccines and rapid diagnostic tests are needed to protect the public from antibiotic-resistant bacterial infections.

"Right now, antibiotic resistance is a very slow-moving train wreck. It might take another decade for antibiotic resistance to become a true disaster, or it might be tomorrow," said Boston University Professor of Law Kevin Outterson, a global expert on the economics of antibacterial R&D and commercialization and executive director of CARB-X. *(See adjacent article.)*

Without effective global action, untreatable infections could cause 10 million deaths globally each year by 2050, according to the *U.K. Review on Antimicrobial Resistance*, commissioned by the U.K. prime minister.

During 2016, the Pew Charitable Trusts determined that only 40 antibiotic candidates were in clinical trials. The antibiotic R&D pipeline is meager because the development and commercialization of these drugs have become unprofitable. Under the current price-multiplied-by-volume economic model, a new antibiotic must be prescribed to the highest possible number of patients for a biopharmaceutical company to recoup its R&D investment and earn a profit. However, the price-volume model has contributed to the inappropriate use of antibiotics, for example, to treat viral infections. Antibiotic misuse and overuse have accelerated the natural evolutionary process by which bacterial strains become resistant.

To slow the development of resistance, a new antibiotic is typically reserved for the relatively few patients whose bacterial infections have proven impenetrable to older antibiotics, many of which are low-cost generics. Public health and insurance company measures that restrict the prescription of new antibiotics obviously decrease their sales. Also limiting antibiotic sales is the acute nature of bacterial infections. Unlike drugs for chronic diseases such as hypertension, antibiotics are usually taken for just a brief time.

Continued on next page

clinical space for antibiotics. CARB-X seeks innovation, not modest modifications of existing products."

In addition to receiving funding, biotech startups awarded CARB-X grants will be given streamlined access to a suite of technical, research, regulatory, and business mentoring services. "Many of these startups are spinoffs of university labs," said Outterson. "While the scientists at these companies are very clever, few of them likely have brought a drug to full FDA approval."

The services will be provided at no cost by CARB-X's partner organizations, ranging from the AMR Center, a private-public translational R&D initiative; to the California Life Sciences Institute (CLSI) and MassBio, two of the world's best biotech accelerators. These and other partners will help shepherd CARB-X funded companies through the preclinical development process. The grantee companies will not be required to use any of the services. If the company enlists its own CRO or another service provider, CARB-X partners "will be happy to work with whomever the company is working with to advance the preclinical development of the product," Outterson said.

For preclinical services and project management support, the grantee companies will be able to turn to the NIAID and AMR Center as well as the nonprofit RTI International, which specializes in project management, clinical trial design, and other services for both government and commercial clients. Outterson gave an example of a service that could be provided by NIAID. If a CARB-X grantee company needs to evaluate its potential product in additional animal models, NIAID will help not only with the model selection but also with the design and conduct of animal testing.

Mentoring and other business support services will be provided by the Wellcome Trust, AMR Center, MassBio (MB), and CLSI. MassBio and CLSI have extensive experience in mentoring biotech startups. "Mentors will help a company decide 'yes' or 'no' on whether a product candidate should progress to clinical trials," Outterson explained. Mentors also will help with IND (investigational new drug) submissions, FDA meeting preparations, and fundraising.

STARTUPS RETAIN IP

To qualify for CARB-X support, a biotech startup must have advanced its product candidate to at least technology readiness level 3, at which proof-of-concept has been demonstrated. The startup also must be a legally established entity with a business structure and sufficient financing separate from the CARB-X grant to support basic operations for 12 months. To finance the development of its products, the startup must provide a cost share equal to at least 20 percent of the project costs. However, CARB-X encourages the companies to propose higher amounts. Because CARB-X grants will be nondilutive, the grantee companies will not be saddled with additional debt or equity dilution. Like NIH grant recipients, CARB-X funded startups will retain their IP.

If the company meets all milestones established by

CARB-X, it will be continuously funded to the end of Phase 1 without having to take time to reapply for funding each year. If a milestone is not met, CARB-X will terminate the company's grant.

CARB-X's three-stage grant application process was up and running within 30 days after the organization established its offices at BU. A total of 350 biotech startups representing 23 countries contacted CARB-X in the first two funding cycles. Since antibiotic-resistant bacterial strains cross borders, CARB-X is not geographically limited in its support of biotech startups with highly promising preclinical antibacterial products.

In addition to Outterson, CARB-X's staff leaders include John Rex, M.D., former senior VP and head

ECONOMIC INCENTIVES RECOMMENDED

During the past decade, several non-U.S. groups including the Review on Antimicrobial Resistance and the Chatham House think tank, both in the U.K., and the EU's DRIVE-AB (Driving Reinvestment in R&D and Responsible Antibiotic Use) have examined various economic incentives to encourage more biopharmaceutical investment in antibiotic R&D. Both U.K. groups have issued reports with recommended incentives. In June 2017, DRIVE-AB will publish its recommendations.

In 2016, the Duke-Margolis Center for Health Policy of Duke University launched a program to create an economic model for antibiotic development that could be integrated into the U.S. healthcare system. "Much of the work of the groups in the U.K. and Europe has been more relevant to the single-payer healthcare system of those countries than to the U.S. healthcare system with its multiple public and private payers," said Gregory Daniel, Ph.D., deputy director and head of the center's pharmaceutical and medical device policy portfolio.

The Duke-Margolis Center brought together a wide range of stakeholders, from biopharmaceutical company leaders to payers, to identify the "push" and "pull" economic incentives that would be practical and effective in the complex U.S. market. "Push" incentives, such as government-funded research grants and public-private R&D partnerships, are designed to reduce a company's financial risks when investing in preclinical and clinical antibiotic development. Examples of these incentives include the biopharmaceutical accelerator CARB-X's research grants and support services for biotech startups with highly promising preclinical antibacterial products.

DE-LINKING SALES FROM REVENUE

One of the most promising "pull" incentives being proposed de-links the sales of a new antibiotic from the utilization of the drug. Instead of sales, the company's revenue would come from financial rewards such as a substantial market entry payment, a transferable exclusivity award, a market exclusivity extension, and milestone payments. A company would earn a market entry award by obtaining regulatory approval of a new antibiotic that met specific innovation criteria such as a novel antibiotic class.

The market exclusivity extension could be used or sold by the company. The dollar value of the award could be large enough to partially provide the market-entry payment, said Outterson. Milestone payments could be a tiered structure of financial awards based on a company achieving specific stewardship benchmarks designed to prevent misuse and overuse of antibiotics as well as ensure availability of the drugs when they're needed. Benchmarks also could include the FDA approval of new indications or different formulations of the antibiotic. Daniel explained that benchmark payments could encourage antibiotic manufacturers to remain engaged in the life cycle of their drugs.

"To be effective, economic incentives must be predictable and guaranteed," said Daniel. "Before making an investment in antibiotic R&D, companies must be confident that the market entry awards and other financial incentives will be available when their new antibiotic products are submitted for FDA approval."

Daniel and other members of his Duke-Margolis team are compiling a white paper proposing a value-based alternate payment model that will provide financial incentives to boost antibiotic development. Once the paper is published, the center will seek input from stakeholders and sponsor a pilot project to identify how the model should be implemented in the U.S.

Continued on next page

THE PROPOSED VALUE-BASED PAYMENT MODEL

A value-based payment model for antibiotics aligns with current trends in the U.S. healthcare system. "We're moving rapidly from fee-for-service to value-based reimbursements based on patient outcomes," said Daniel. While the details have not yet been worked out, the center's economic model likely will require a phased-in approach to value-based reimbursement, he said.

The Duke-Margolis model will propose a market-entry award paired with value-based payments from contracts that the biopharmaceutical company would negotiate with private payers. The base market-entry payment could total $200 million during the first year after regulatory approval. In subsequent years, the market-entry payment would lessen and be based on a company demonstrating an increasing percentage of revenue coming from its value-based contracts with private payers.

"This would limit the size of the market-entry reward needed, incentivize movement toward more payments based on value, and ensure that payers aren't paying any more than they usually do for antibiotics," said Daniel. In this model, payers will structure their payments based on their membership size rather than the volume of the drug used. Payments also would be based on the availability of the drug and the biopharmaceutical company's support of stewardship.

Whether the U.S. government will totally or partially fund the market-entry award has not been determined, and the Centers for Medicare & Medicaid Services' role in this proposed model also has not been defined.

To delay the development of bacterial resistance to its antibiotic, a company must be "thoughtful about stewardship from the word go," said Outterson. "From society's standpoint, we want a new antibiotic to remain effective for 50 to 100 years – well beyond its patent life."

Daniel said that "ideally a company will put its new antibiotic on a shelf and distribute it only when it is really needed."

Stewardship and de-linkage of an antibiotic's revenue from its utilization are major components of the economic models drafted by U.S., U.K., and E.U. groups. The models are similar in recommending a comprehensive strategy of "push" and "pull" incentives, global coordination, and access to antibacterial drugs at a reasonable price in developing countries. "While there is widespread inappropriate or excessive use of antibiotics in the U.S., there are many countries where people cannot afford antibiotics when they need them," said Outterson.

Biopharmaceutical companies have expressed support for new economic models for antibiotic development and commercialization. In early 2016, more than 80 companies signed the Davos Declaration, which called on governments to help develop new and alternative market structures providing incentives for investing in antibiotic R&D. Prior to the United Nations General Assembly's high-level meeting on antimicrobial resistance in September 2016, 13 companies presented a new road map with four key commitments to reduce antimicrobial resistance. Among their commitments is "establishing new business models that balance access needs, appropriate antibiotic use, expanded vaccine coverage, and adequate return to companies."

of infection in global medicine development at AstraZeneca. Dr. Rex, chief strategy officer at CARB-X, also is a voting member of the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria. Barry Eisenstein, M.D., who heads CARB-X's science advisory board, was senior VP of scientific affairs at Cubist Pharmaceuticals, now part of Merck. CARB-X's Global R&D Director Karen Gallant, Ph.D., was global head of business development for AstraZeneca's infection, neuroscience, and gastrointestinal programs. In addition to these staff leaders, CARB-X's executive team includes 23 representatives of partner organizations, none of whom receive salary support from CARB-X.

By 2021, if CARB-X's plans prove effective, the currently sparse global clinical antibacterial pipeline will be enriched by several novel antibiotics, vaccines, and rapid diagnostic tests ready for clinical testing. L

Update: CARB-X recently announced that it awarded grants to 11 biotech companies and research teams. The grants total $24 million up front and promise up to $24 million in milestones.

Where Others Have Failed, Genocea Sees Promise In T-Cell Vaccines

MIKE GOODMAN Contributing Writer

Genocea Biosciences is at the forefront of companies harnessing T-cell immunity to conquer the most difficult infectious diseases. Founded in 2006 with antigen discovery technology out of Harvard University, the Cambridge, MA-based company has spent the past decade progressing GEN-003, an HSV-2 (genital herpes) therapeutic vaccine, through the clinic and launching a personalized cancer vaccine franchise that will file its first IND (investigational new drug) this year and enter the clinic in 2018.

Genocea says its antigen discovery platform, ATLAS, is the key to its success in developing T-cell vaccines. An antigen is a target on which vaccines or immunotherapies act to elicit an immune response. While other vaccine companies have tried to identify T-cell antigens by using predictive algorithms or by taking a guess, the ATLAS approach is based on natural human immune response observed in large, diverse populations.

While Genocea focuses on identifying the right target antigen, and its HSV-2 T cell vaccine is in Phase 3, several small-cap biotechs and some large-cap vaccine players appear to have abandoned their programs.

THE VACCINE MARKET: GROWING AND BUBBLING WITH M&As

The global vaccine market is growing at a CAGR of about 10 percent, far outpacing drugs and medical devices. We asked Genocea CEO Chip Clark whether he thought the vaccine market could sustain its torrid growth. "I do think it can continue to be robust for a couple of reasons. First, there remain many pathogens, such as those requiring a T-cell response, for which we don't yet have good vaccines. And secondly, there are new ideas about what a vaccine is and where it can be useful." Clark is referring to the revolution in immuno-oncology that is based on unleashing the power of T-cells to kill tumors. "We believe," he says, "that personalized, so-called neo-antigen vaccines can be an effective complement to checkpoint inhibitors that have been approved to treat cancer."

The vaccine market is also a hotbed of M&A activity. GSK, for instance, spent $7.8 billion in 2015 on Novartis' vaccine business, while Pfizer spent north of $1.2 billion over the past three years, picking up vaccines from Baxter and GSK as well as acquiring RedVax AG, a spin-out of Swiss vaccine specialist Redbiotec AG.

Genocea's ATLAS technology and its Phase 3-ready HSV-2 candidate position it for a potential acquisition. Although Clark doesn't rule out a buyout, he is more focused on finding a partner for GEN-003 before it enters Phase 3. He feels the time is ripe, having just released placebo-controlled lesion rate data at six months post dosing from GEN-003's Phase 2B trial. In addition, the Phase 3 dose is set, and the company has a primary endpoint. "We think we have a package in hand that would be compelling to potential partners."

Clark believes there are a number of ways the company can think about sharing its assets and technology. "The best solution will be one that provides the right intersection between furthering our goals — assuring that GEN-003 gets approved as widely and rapidly as possible — and maximizing shareholder benefit." He would be open to a single global partnership or one that split the world into a couple of territories, say, U.S. and rest of world. Either option would admit a broad range of bidders. Clark is basically looking for a partner with sufficient financial resources and complementary capabilities (e.g., global regulatory, global clinical development, global commercialization). He's also interested in

a partner with experience selling to some of the key call points for GEN-003. For instance, in the U.S., and less so in Europe, that would be OB-GYN physicians.

THE INVESTMENT LANDSCAPE FOR VACCINES

The funding of vaccine development and, in less-developed countries, vaccine distribution is quite different from the funding of drugs or medical devices. In most cases, the primary investor is a public entity or increasingly public/private vehicles. Venture capital is largely absent from the financing or creation of vaccine startups.

Clark thinks the reason that VC has kept away is that the new wave of T-cell vaccines present novel technology challenges. Looking over the past century of vaccine development, there have been significant successes — flu, measles, and mumps — but there has also been a flattening of the return curve. Clark explains, "We now have vaccines that can prevent infections caused by roughly 40 different pathogens. But that's the low-hanging fruit. Most approved vaccines work through B-cell responses, but the pathogens of many diseases such as HSV or EBV (Epstein–Barr virus) are largely invisible to disease-fighting antibodies. That's because they are in places where T-cells can go but antibodies cannot." Genocea claims to have the only validated platform for finding the right target antigens of T-cell response. Technologies like ATLAS for discovering T-cell antigens, and novel adjuvant delivery systems, are all quite new. Clark feels that VC investors are waiting for more decisive validation before jumping in.

READY FOR THE FUTURE

GEN-003 has been through a rigorous Phase 2 program designed to demonstrate its activity against the genital herpes virus and to home in on the safest, most effective dose of antigen and adjuvant. These trials have shown that GEN-003's ability to reduce viral shedding (when the virus is active and shedding at the site of infection) and lesion rates is durable (i.e., shown efficacy) out to 12 months. Genocea believes GEN-003 can capture much of the HSV-2 market — a global peak $2 billion opportunity — currently held by the generic oral antivirals famciclovir, valacyclovir, and acyclovir. These drugs are often used episodically to treat HSV-2 outbreaks; however, infected individuals continue to shed, or transmit, the virus even when they are asymptomatic. An HSV-2 vaccine administered once each year would reduce viral shedding continuously. Compliance would be greatly improved.

Genocea's three major assets — ATLAS, the infectious disease pipeline, and the cancer vaccine pipeline — are rapidly evolving. Now all eyes are on its HSV-2 candidate. But its three cancer research collaborations — with Dana Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Checkmate Pharmaceuticals — are all based on the ability of ATLAS to discover antigens of T-cell response.

What if in the next five years ATLAS' capabilities became more in demand by research institutions and Big Pharma? Or if the neo-antigen cancer vaccines started showing eye-popping data? Would Clark consider reorganizing the business around such a development?

He feels that in five years GEN-003 should be on the market, and a cancer vaccine could be near an approval decision. "We're always thinking about the best use of Genocea resources, whether it's to develop the assets on our own, to partner them, or to sell the company. And the way to solve for that is to look at value, time, and risk, and to solve for the right outcome. I can't forecast where we'll be in five years, but I think we'll have great options."

For the rest, Genocea meets with the FDA this quarter to plan for GEN-003's Phase 3 trial; it expects to initiate the pivotal trial in the fourth quarter of 2017. The company is confident the FDA will accept its lesion-rate data as a primary endpoint instead of the recurrence-free endpoint used by the current standard, the oral antivirals. "It's not just about whether you've had an outbreak," notes Clark, "it's about whether you've had a durable reduction in the number of days with lesions."

Clark points to Cubist as a company to emulate. "They were smart drug developers," he says, "and they had a unique and compelling work culture. Those are two things we've strived to focus on as we've built this company."

> *"We believe that personalized, so-called neo-antigen vaccines can be an effective complement to checkpoint inhibitors that have been approved to treat cancer."*
>
> **CHIP CLARK**
> CEO, Genocea Biosciences

Pharma Embraces The Cloud ... **Cautiously**

GAIL DUTTON Contributing Editor @GailLdutton

Pharmaceutical companies that have, until recently, eschewed cloud computing are migrating applications into that environment. Adoption began gradually, first with functions that aren't mission-critical. After a few years' experience, they're still cautious, seeking to adopt the cloud strategically while minimizing risks.

Santen, a Japanese pharmaceutical company specializing in ophthalmology, uses the cloud-based SAS data analytics platform to collaborate with its global team of programmers, statisticians, and scientists. "We wanted a centralized location for all our data from all of our sites," says Nina Worden, director of statistical programming at Santen.

As a benefit, "Everyone is working off the same version of the data. Study results can be combined for exploratory analysis, eliminating the need to email snapshots of data with updates later." Consequently, charts, graphs, and reports are more current and accurate.

The Software as a Service (SaaS) model Santen uses from SAS offers the ability to assign levels of access to specific individuals or groups. "For example, we can permit access to a single file without also giving a user access to all the contents within its folder. Our CRO in China, for instance, has contractor access, while our own programmers in California have slightly higher access," Worden explains.

The analytics application is 21 CFR Part 11-compliant, which allows audit logs and version control for documents. "Each modification to a program is logged by the system, and reports can be produced to document these changes."

Learning the UNIX operating system was the main challenge for Santen's team as it migrated analytics from its Windows-based PC SAS application (which ran on a server) to the cloud-based SAS application. "My programmers had to get used to minor coding differences," Worden says. Likewise, managers needed to learn how the application was structured in terms of storage allocations for development and production space. Sometimes new processes had to be created to manage those areas efficiently.

> *"Some of our smaller operations and marketing analytics projects have leveraged the cloud."*
>
> **ANDY NEWSOM**
> SVP & CIO, CSL Behring

For example, the development system, production area, and repository are each separate, which effectively partitions storage. Managers need to be aware of that when they allocate space. They also need to be aware of where data is stored to ensure, for instance, that classified data isn't stored on virtual servers with lesser security protections. Other changes included new data-handling processes that enabled allowed portions of studies to be reviewed and new rules on when or whether data could be downloaded from the SAS cloud.

Any inconvenience was more than offset by gains in efficiency and oversight. Creating a centralized database that is available to researchers at all of Santen's sites virtually guarantees that, as datasets evolve, analysts are working with the most current versions.

Throughout the organization, Worden says, "Results are more consistent."

The single system also helps Worden manage projects across the enterprise. Using a single application makes it easier for developers to create macros and tools they can share with colleagues at other sites. Therefore, "with programmers in China, Japan, and California, we can hand off tasks across time zones so the work continues, nearly around the clock."

Santen has been in the cloud for approximately five years, but "we've really seen the benefit in the past three years, when we added our sites in China and Japan to the cloud. Adopting cloud computing has broadened our ability to be truly global and more efficient," Worden says. "It helps us foresee possibilities beyond our core mission. For example, we could use the cloud as a combined area for studies and to conduct exploratory analysis that could shape the design of a future study in a way that streamlines data mining."

CSL BEHRING'S PLAN TO MIGRATE TO THE CLOUD

"Cloud computing is gaining traction in pharma," acknowledges Andy Newsom, SVP and CIO at CSL Behring. Pharmas of all sizes are trying to leverage the cloud's value while ensuring data security and integrity. Typically, that means minimizing risk by first deploying noncore functions such as HR and purchasing.

"Some of our smaller operations and marketing analytics projects have leveraged the cloud," Newsom says, and larger projects might enter the cloud after the company's policies regarding Big Data analytics are further defined. GxP data, however, will remain on premises — not in the cloud — for the foreseeable future. That's in line with the pharma industry, he says.

Before migrating any application to the cloud, CSL Behring performs an on-site audit of the cloud provider. This involves ensuring the provider's certifications are current and assessing risks and vulnerabilities in technologies, processes, and staff, and the adequacy of protocols and controls. (Audit guidelines are available from organizations such as the Cloud Security Alliance and the National Institute of Standards and Technology.)

Before the cloud was adopted, purchasing a new HR application, for example, was a capital expense. In a cloud environment, however, that HR application is an operating expense that manifests as an annual subscription fee (which can't be depreciated). Finance departments treat those cost categories differently and apply different governance guidelines. "Companies are struggling with this difference," Newsom says.

CLOUDS ENHANCE SECURITY

Cloud computing comes in three basic varieties:

- Infrastructure as a Service (IaaS) – Infrastructure for a virtual computing environment
- Platform as a Service (PaaS) – IaaS plus the operating system and server software for a development environment
- SaaS – IaaS, PaaS, and specific user-facing applications

"The largest cloud providers [e.g., Amazon and Microsoft] provide security and data protection that is as good as or better than the security provided by the IT functions in other industries," Newsom says. In addition to their deep expertise, cloud providers rigorously install software updates and security patches – tasks their prospective clients too-often ignore.

Cloud providers enhance standardization within clients' organizations, too. By allowing configuration but not customization, cloud deployments help pharmas ensure that all their sites are technologically compatible. Therefore, data can be shared within the enterprise without having to convert it to other formats. At the application level, SaaS providers update their applications so users don't have to.

LIABILITY CAN'T BE OUTSOURCED

"The disconnect between the cloud and pharma is philosophical," according to attorney Gerry Stegmaier, partner in the privacy, data security, and internet strategy practice at Reed Smith. Often the conversation involves a list of needs by pharma and a list of specifications by cloud providers, without an understanding of the extent to which those specifications actually meet pharma's needs.

"Companies are responsible for the integrity of their data regardless where it's stored," Newsom points out, and relying on another entity to protect it makes pharma executives nervous.

The financial industry was in that position seven years ago, concerned about regulations and fiduciary liability. "Cloud providers heard those concerns and adapted. In the past two years, cloud providers developed HIPAA-compliant services for healthcare clients. Now they are beginning to address the needs of pharma," Stegmaier says.

Pharma's acceptance of cloud computing, even for mission-critical applications and data, is inevitable. Stegmaier calls it "an eventuality." Migration, however, will continue gradually as more and more pharmaceutical companies realize the benefits of cloud computing in ancillary business functions before entrusting mission-critical work to the cloud.

"If, as a company, you're betting against the cloud, you'll be on the wrong side of history," Stegmaier concludes.

Compassionate Use: The Family & Patient Perspective

JULIE DEARDORFF, PH.D., MPH Contributing Editor

"The one thing I wish could have been different with the compassionate use program is that I would have known about it earlier," says Nicole Pierson. Nicole's son Gavin, who was diagnosed with a rare brain tumor when he was 5 years old, is alive today because he received IBRANCE (palbociclib) via compassionate use from Pfizer. Although IBRANCE didn't cure him, it did prolong his life long enough until a new type of laser technology became available which ablated his tumor.

Nicole considers her family lucky that Gavin survived long enough to be able to participate in the compassionate use program. She had done more than her fair share of diligent research — she educated herself tirelessly on her son's disease, including learning about the specific markers of her son's rare tumor. She also researched the available treatments as well as the new ones being investigated in clinical trials, becoming very familiar with sites like pubmed.gov and clintrials.gov. She just knew that IBRANCE would work for Gavin, but he didn't meet the inclusion/exclusion criteria. However, then her physician said they could try applying for compassionate use. "I knew about clinical trials, but I had never heard of compassionate use until it was almost too late," she says. If she would have known about the compassionate use program, she would have applied for it six months earlier. With a disease like Gavin's, six months could have been too long. Nicole said though, once she found out about compassionate use, the process went very smoothly. The company was very helpful, and it was less than four weeks from when she found out about the program to when Gavin received the drug. She is very grateful that Pfizer took a chance, especially given that IBRANCE had never been studied in the pediatric population.

When asked about her concerns about using a drug that hadn't been approved yet and for which the safety profile in a patient such as Gavin had not been established, she said it was worth the risk. They had tried everything (five craniotomies among other treatments), and it's not as if the standard of care for Gavin's disease wasn't associated with significant risks. "I knew after the first 20-hour craniotomy had removed only 20 percent of his tumor that the standard of care was not going to work. In his case, the standard of care was so risky and associated with such significant side effects that we were lucky that he survived so many surgeries." So in cases like this, her thought was: Why wait until the standard of care has failed so miserably and caused so many side effects that the patient doesn't even stand a chance of tolerating further treatment?

Karen Laughlin, Ph.D., who has helped form the nonprofit CURe (Compassionate Use Reform) which is dedicated to the avocation of compassionate use, couldn't agree more. She feels the first step that can be taken to support patients is to increase awareness. She believes when a patient is told they have a terminal disease, they should be informed of all treatment avenues from the very beginning. The initial treatment consultation should explain that there is the standard of care, and if that fails clinical trials, and if a person doesn't meet the criteria for the clinical trial, then compassionate use is an option. In that way the patient can evaluate their treatment success/failure and determine when/if they might want to try a different avenue.

From its research, CURe has found that the bottleneck to compassionate use is company approval. CURe acknowledges that companies have valid concerns such as the patient experiencing potential adverse

events or death, economic concerns (including supply constraints), and ethics pertaining to access. From 2011-2015, of the 1,210 requests submitted on average annually, the FDA approved 99%. However, that number only represents requests to which companies had said yes. We don't know how many patients hear "no" from a company. Unfortunately, patients do not always trust that the reasons they are hearing for "no" are really legitimate. Thus, Laughlin feels to engender trust from the patient's side, there's a need for more transparency and consistency so that patients feel that their request has been handled fairly. After all, if you or your loved one has tried everything available and is desperate to live, it's very hard to hear no.

"The one thing I wish could have been different with the compassionate use program is that I would have known about it earlier."

NICOLE PIERSON
Son was diagnosed with a rare brain tumor when he was 5 years old

CURe wants to bring all sides together, such as policy makers, health organizations, regulatory authorities, pharmaceutical representatives, and patients, to identify the biggest barriers so compassionate use can work better for everyone and that companies "increasingly and more consistently say 'yes' when it's medically appropriate and logistically feasible." Laughlin notes that all parties agree that compassionate use should not compromise ongoing clinical trials and, thereby, the greater public good. She acknowledges the complexity of the issue, thus, more the reason to pull all players together, including those in other sectors (e.g., clean energy experts and tax strategists), and harness new design approaches out of Silicon Valley to develop practical innovative solutions such as tax credits that would benefit companies and increase their motivation to increase access.

One change she'd like to see is companies considering their compassionate use program from the get-go, not after they start receiving requests. She points to steps taken by Johnson & Johnson as pioneering. The company has established a third-party ethical leadership board dedicated to review compassionate use requests made to the Janssen Pharmaceutical Companies. If boards such as these could be more the norm than the exception, that would be great, especially when they incorporate the patients' views as well. For example, one ethical concern she has heard from companies is that patients really don't understand the risks of a compassionate use program. However, she says that based on CURe's experience with patients, this shouldn't be a roadblock. Patients sign waivers to participate in traditional trials, so this is not foreign and, most importantly, many are "viscerally aware" of the risks of treatments as many approved treatments are associated with considerable side effects and risks, including death. Thus, one of CURe's top priorities is for companies to develop consistent policies that are based on guidance that has been stripped of such misperceptions. She hopes that CURe can be a critical resource and help facilitate the process.

Although CURe is not promoting this stance, it can be easy to see the call to expand compassionate use as a patient-versus-pharma situation. However, it's important to remember that with compassionate use, patients and pharma companies are both taking risks. But according to Christine Brown, Ph.D., a lead investigator on a Phase 1 study being conducted on glioblastoma at the City of Hope, the risks taken by both sides can lead to a win/win situation in certain cases. For example, recently Rich Grady, a patient with recurrent glioblastoma, was granted compassionate use of a novel route of delivery that wasn't an option in the existing trial. The result was two-fold: He experienced a remarkable complete remission, and information from his responses has been used to amend the ongoing protocol so this delivery system can be provided to others. His wife said that, although the treatment was not a cure, it gave them more than an extra year of relatively high quality of life together. They are at peace with their decision, and "they hope that information gained will help many people live longer and healthier lives." That is a goal everyone can agree with. L

Educating Consumers About The Risks Of Counterfeit Medicines

CAMILLE MOJICA REY Contributing Writer

This is the final article in a four-part Life Science Leader *series examining the current state of the counterfeit medicines problem. Previous stories looked at efforts to quantify the crime, examined the issue from the perspective of industry giant Pfizer, and described what is being done by an international coalition to fight the crime.*

In 2016, the Alliance for Safe Online Pharmacies (ASOP Global) estimated that 20 rogue online pharmacies are launched every day. Unsuspecting patients do not realize that 96 percent of these sites are bogus. They risk their health if the pills have no active ingredients or contain deadly ingredients. They put themselves at risk of identity theft. They also unknowingly fund organized crime and terrorists.

The pharmaceutical industry has created or joined numerous local, national, and international partnerships to combat the problem of rogue pharmacies. Their partners include the likes of large corporations, such as Google and Microsoft, as well as pharmacy groups, medical associations, and patient advocacy groups.

"I see improvement in industry efforts to stop counterfeiters, but I don't see improvement in results," says Marvin Shepherd, president of the Partnership for Safe Medicines (PSM) and professor emeritus at the University of Texas at Austin's School of Pharmacy. PSM and other organizations like it have been working to teach people how to safely buy drugs online and identify illegal online pharmacies and point them to programs that help pay for their medicines so they don't go looking for them online.

These nonprofit groups have their work cut out for them. A 2015 study by pharmaceutical giant Sanofi estimated that 88 percent of Americans were unaware of the dangers of counterfeit drugs. Nonprofits working to educate the public have been busy producing awareness campaigns, building educational websites geared for patients, and targeting advertising to consumers through search engines.

In 2014, the National Association of Boards of Pharmacy (NABP) started making it easier for consumers to find legitimate pharmacies online by launching .pharmacy as a Top-Level Domain (TLD). NABP evaluates these sites and certifies those that are found to be in compliance with pharmacy laws and meet standards for pharmacy practice, as well as patient safety.

A NEW WAY TO REACH CONSUMERS

The challenge for NABP and others is to get their message out so that patients understand the risks and know how to stay safe online. ASOP Global has taken many traditional approaches to reaching consumers, including social media and placing a television PSA in New York's Times Square. "None of it has been enough," says Libby Baney, ASOP Global's executive director.

ASOP Global is trying a new way to reach patients: targeting their doctors, nurses, and pharmacists instead. "Healthcare providers are critical to the education of healthcare consumers," Baney says. However, according to data collected by ASOP Global in 2016, only 6 percent of providers surveyed ever discussed the risks of rogue online pharmacies with their patients, and nearly 95 percent of them did not know how to identify illegal online drug sellers.

In 2015, ASOP Global and the Federation of State Medical Boards (FSMB) launched a program that

includes a free continuing education course, "Internet Drug Sellers: What Providers Need to Know," for doctors, nurses, pharmacists, and other healthcare providers. "ASOP Global hopes to educate providers about the dangers of illegal online pharmacies so they, as the most trusted resource to patients, can help consumers avoid the health and financial risks associated with buying counterfeit products online," Baney says. Pilot studies showed that 81 percent of healthcare providers who took the course said they would now include discussions of the risks posed by rogue online pharmacies with their patients.

In December, ASOP Global launched www.BuySafeRx.pharmacy, a site where providers, patients, and caregivers can quickly verify whether an internet pharmacy website is safe and legal. The organization has also partnered with the American Medical Association, American Pharmacists Association, and 14 other national nonprofit organizations to deliver educational materials and content to offices through websites and on social media. "We are looking for the best ways to reach providers," Baney says.

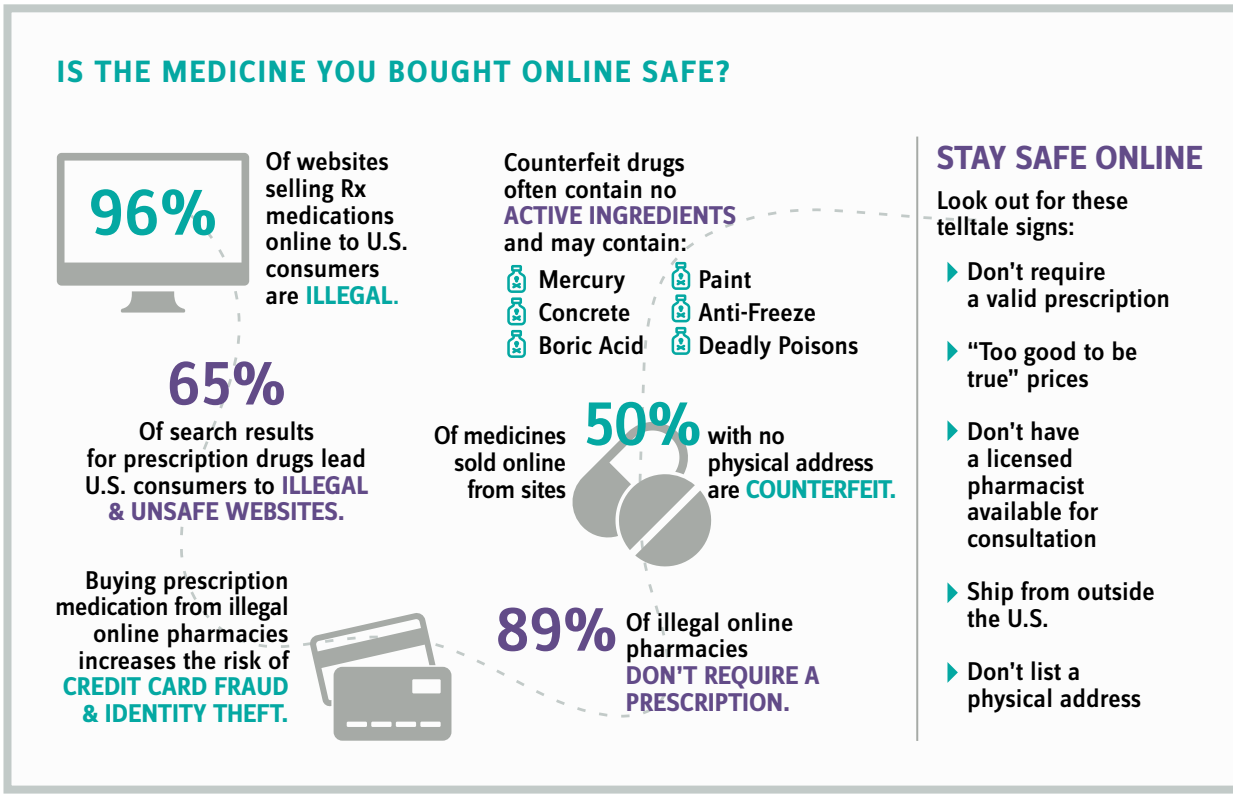
ADAPTING TO NEW THREATS

Raising awareness among physicians goes beyond educating them about online risks so that they can inform patients. Doctors also need to know that there are criminals posing as patients. "What happens is that consumers will sell leftover drugs — or ones they never needed in the first place — to diverters," PSM's Shepherd says. Diverters repackage pills, sell them locally, or send them to a fraudulent wholesaler. Once they are repackaged, the drugs are considered counterfeit. The diverter stands to make $500 on the same prescription that cost the person posing as a patient $20 or $30.

In 2012, PSM published online toolkits for both healthcare providers and patients. The one for healthcare providers gives tips on spotting counterfeits, looking into the possibility that drug treatments are not working because they may be fakes and educating patients about the risks of online pharmacies. Future efforts by PSM and others will have to include educating doctors on new ways they may be targeted by criminals, Shepherd says.

The global use of unique identifiers is expected to be in place in the next few years. These bar codes will help combat pharmaceutical crime at all levels of the supply chain, but they will not be enough, Shepherd says.

Emerging technology that would allow the marking of individual pills may be the answer. Such methods are worth investigating, Shepherd says, because pharmaceutical crime is here to stay. "What you have to do is try to control it. You have got to stay one step ahead of the thugs." L



Biopharma IPR Trends

MICHAEL SIEKMAN AND OONA JOHNSTONE, PH.D.

It has been almost five years since post-grant proceedings, including inter partes reviews (IPR), were implemented under the America Invents Act as an alternative to patent litigation for challenging granted patents. Taking place before the Patent Trial and Appeal Board (PTAB) at the U.S. Patent and Trademark Office, these proceedings quickly gained the reputation of being patent "death squads," because they resulted in surprisingly high rates of patent cancellation and therefore became a complement to most patent litigations.

While biopharma patents initially represented a small percentage of post-grant proceedings, that percentage has been increasing. In particular, generic and biosimilar manufacturers are taking advantage of these proceedings, not just as a complement to litigation, but also to clear patents covering brand-name drugs and biologics before litigation occurs.

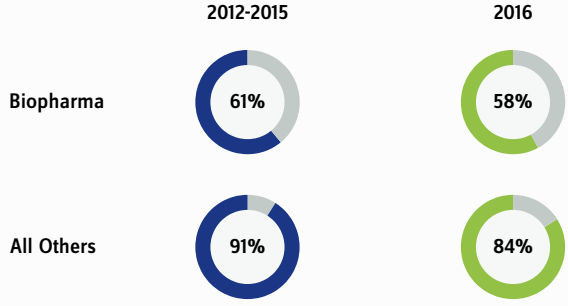
POST-GRANT STATISTICS ACROSS INDUSTRIES

Biopharma represented 13 percent of post-grant petitions filed in 2016, up from 9 percent in 2015. There are likely several reasons for this relatively low percentage. IPRs are often filed concurrently with litigation, so the filing rates tend to be highest in the more litigious technology areas, such as electronics. Also, the timeline for bringing a drug or biologic to market is lengthy, so post-grant proceedings in biopharma tend to be part of a long-term business strategy in which there may not be the same immediate time pressure to file quickly that exists in other industries. Finally, IPRs are limited to prior-art grounds, and only certain ones at that. A separate category of post-grant proceedings called post-grant review (PGR) — which allows for challenges on all patentability grounds, including patent-eligible subject matter and sufficiency of description, which tend to be highly applicable to biopharma inventions — is just starting to become available. Accordingly, we can expect to see a significant increase in biopharma post-grant proceedings in the coming years.

In general, post-grant proceedings have been highly successful for petitioners. However, the statistics have been less favorable for petitioners in biopharma than in other technologies. This trend can be seen in part at the institution stage, when the PTAB decides whether to initiate a post-grant trial. For biopharma petitions that reach this stage, the institution rate is approximately 63 percent, compared with 71 percent for all other technologies combined. Significantly, this trend is even more apparent at the final written decision stage. In biopharma, from 2012 to 2015, for petitions that reached this final stage, approximately 61 percent resulted in at least one claim being found unpatentable, with the percentage dropping slightly to 58 percent in 2016. By comparison, in all other technologies combined, from 2012 to 2015, a striking 91 percent of petitions that reached this final stage resulted in at least one claim being found unpatentable. While this percentage dropped slightly in 2016 to 84 percent, it is still significantly higher than in biopharma.

Accordingly, biopharma patent owners can take some solace in the fact that their patents appear to be more readily able to withstand IPR challenge than patents in other technology areas. This is primarily due to the recognized unpredictability in biopharma. Obviousness analysis plays a critical role in biopharma post-grant proceedings, and patent owners have been successful in using unpredictability to their advantage by arguing lack of reasonable expectation of success in achieving biopharma inventions.

PERCENTAGE OF FINAL WRITTEN DECISIONS IN WHICH SOME OR ALL CLAIMS FOUND UNPATENTABLE



SOURCE: Lex Machina. All post-grant petitions filed in Technology Center 1600 were classified as biopharma

ADVANTAGES OF IPR FOR GENERICS AND BIOSIMILARS

Post-grant proceedings, such as IPRs, present multiple advantages over litigation for parties wishing to challenge a biopharma patent, such as generic and biosimilar manufacturers. In particular, the proceedings are decided by a panel of Administrative Patent Judges (APJs) who are highly technically trained and more comfortable finding patents unpatentable, as opposed to a district court judge and jury. This can be especially relevant in complex technical areas, such as biopharma, where decisions on patentability frequently rest on obviousness analysis (i.e., analysis of whether the claimed invention would have been obvious to one of ordinary skill in the art) including interpretation of secondary considerations where APJs have proven skeptical of patentees' arguments. Relative to litigation, petitioners in post-grant proceedings also benefit from a broader standard for claim construction ("broadest reasonable interpretation"), a lower standard of proof (preponderance of the evidence instead of clear and convincing evidence), and a related lack of presumption of patent validity.

Post-grant proceedings are also generally considerably faster and less expensive than litigation and can be filed by essentially any entity (other than the patent owner). Additionally, courts frequently stay concurrent litigation pending the outcome of a post-grant proceeding, since the result of the proceeding can simplify, or even eliminate, the issues needing to be litigated.

INSIGHTS FROM EARLY GENERIC IPR CHALLENGES

Multiple IPRs filed by generic manufacturers have now reached final written decisions. While the first series of decisions favored the patent owners, the results have since shifted somewhat to favor the petitioners, indicating that in some instances, generic manufacturers are succeeding in using this approach to eliminate blocking patents.

Noven Pharmaceuticals, Inc. and Mylan Pharmaceuticals Inc. v. Novartis AG and LTS Lohmann Therapie-Systeme AG

These IPRs represent an example where generic manufacturers successfully used IPRs to cancel claims that had previously been found to be patentable in litigation. Noven and Mylan challenged two patents covering the Exelon patch, marketed by Novartis for treatment of dementia. Both patents had been litigated at least once in district court and on appeal at the federal circuit, with each court upholding the validity of the patents. Significantly, when Noven and Mylan challenged the same patents in an IPR, the PTAB reached the opposite conclusion, finding all the challenged claims unpatentable and noting, in part, the different standard of proof in an IPR relative to litigation.

Mylan Pharmaceuticals Inc. and Amneal Pharmaceuticals LLC v. Yeda Research and Development Co. Ltd.

These IPRs represent an example where generic manufacturers successfully used IPRs to clear blocking follow-on patents. Mylan and Amneal challenged three patents covering "3-times-a-week COPAXONE 40 mg/ml," marketed by Teva. The challenged claims were directed to methods of treating multiple sclerosis by administering three 40 mg injections of Copaxone over seven days. The PTAB determined the claimed dose regimen was obvious over prior art that disclosed administering 40 mg doses of Copaxone every other day. While the PTAB acknowledged a presumption of a nexus between the drug's commercial success and the claimed dose regimen, it found that the petitioner overcame this presumption by showing that, rather than being attributed to superior properties of the claimed invention, commercial success was largely a result of brand recognition combined with aggressive marketing and substantial price discounts aimed at outcompeting generics of the original version of Copaxone. L

See the extended online version of this article to read about examples of early biosimilar IPR challenges and key takeaways. | LifeScienceLeader.com

MICHAEL SIEKMAN is a shareholder in the Biotechnology and Post-Grant Proceedings Practices at intellectual property law firm Wolf Greenfield in Boston.

OONA JOHNSTONE, PH.D. is an associate in the Biotechnology and Post-Grant Proceedings Practices at intellectual property law firm Wolf Greenfield in Boston.

Is The Cuban Biopharma Industry A Forerunner Of Pharma 3.0?

Part 1

ANDRÉS CÁRDENAS-O'FARRILL

Pharma 3.0 is gradually becoming the new paradigm in the healthcare industry among scholars, industry experts, and practitioners. This new approach is said to be the result of significant healthcare reforms in key pharmaceutical markets in the wake of the many challenges faced by the industry (e.g., low R&D productivity, tighter capital environments). But what's peculiar is that this new trend, or at least a significant part of it, might find a distinguishable, if somewhat neglected, forerunner in the Cuban biotech industry. That may sound far-fetched at first, but let's take a closer look to see if there are some plausible explanations.

Cuba has become a recognizable southern leader in the biopharmaceutical industry and has pharmaceutical export partnerships with more than 50 countries. According to BMI Research, exports include 30 innovative medicines manufactured only in Cuba.

The country's biopharma industry has been successful in a number of indicators, ranging from cash flow and profit margins to return on investment. Although the pervasive lack of data still makes it difficult to confirm this assertion, the available evidence demonstrates the industry's achievements. This applies not only to the profuse generation of products (biopharmaceuticals and vaccines), which cover more than 60 percent of the local demand, but also to the successful impact on public health.

PHARMA 3.0: A SEARCH FOR SUSTAINABLE HEALTHCARE

The approach and definition of Pharma 3.0 were introduced in *Progressions 2010: Pharma 3.0*, a report produced by Ernst & Young in 2010. While Pharma 1.0 and Pharma 2.0 were based on blockbuster drugs and diversified drug portfolios, respectively, Pharma 3.0 focuses on health outcomes. Where the former models emphasized proprietary knowledge and short-term bottom-line returns, Pharma 3.0 stresses open collaboration platforms and long-term partnerships with nontraditional players in order to gain access to underserved markets.

These reports have gradually recognized the structural problems of those previous models and have referred to them as the main reasons behind the productivity and innovation challenges faced by the industry during the past 40 years. This situation became more explicit after the financial downturn of 2008, which put in evidence the unsustainable character of the biopharma business model.

> *"Cuba has become a recognizable southern leader in the biopharmaceutical industry and has pharmaceutical export partnerships with more than 50 countries."*

Among the most relevant global reforms that sparked discussion of the new model are efforts to boost primary care and increase access in rural areas, to target basic diseases, and to introduce low-priced generics (emerging markets). At the core of these reforms is the need to expand equitable and afford-

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able access while still containing healthcare costs. These reforms are emblematic of a global trend to achieve *affordable* healthcare.

In Pharma 3.0´s philosophy, to be successful producing drugs in the long term requires taking care of the highest possible number of people by addressing their real medical needs. The focus is on areas such as disease prevention, data sharing, long-term health outcomes, seeking unmet needs, community engagement, holistic thinking, and health information technology. In this new model, innovation not only drives drug development, but ensures those drugs can contribute to the general well-being. In fact, many of Pharma 3.0´s basic tenets were adopted by the Cuban biomedical ecosystem long before this new business model was conceived.

CUBAN BIOPHARMA PART OF A BROADER PLAN

Neither the achievements of the Cuban biopharmaceutical industry, nor its existence, can be explained without considering the industry as being part of a broader strategy, aimed primarily at finding cost-effective solutions to local healthcare. Cuba's biotech success in accomplishing this goal has made it possible for Cuban companies to further capitalize their achievements into commercial opportunities by entering the global market as low-cost producers of high-quality products.

The Cuban industry has a history of developing and manufacturing many innovative products. Indeed, the inception of the Cuban biotech industry is linked to Interferon (IFN-α), the first recombinant product obtained by a group of Cuban researchers in 1981 after receiving training in Houston and Helsinki, Finland. Cuban scientists quickly grasped the benefits of this substance for treating internal bleeding caused by dengue fever, a disease that was seriously hurting the country during the 1980s.

The same goes for VA-MENGOC-BC, the first commercially available vaccine for serogroup B meningococcus. Developing the product became the priority for the health system after a severe epidemic of meningitis reached frightening heights in Cuba from 1982 to 1984. Add the stories of Quimi-Hib, the world's first synthetic vaccine against Haemophilus influenzae type b, or Heberprot-P, a novel and unique Cuban biomedicine for treating diabetic feet, and you will find the same kind of commitment toward improving health outcomes.

Cuba's biotech industry is based on a deliberate integration agenda. First, the most important companies of the sector work following what industry officials call a closed loop, which means the in-house completion of all products' development phases. At the same time, almost every product developed by the industry is the result of joint efforts of several companies. There is no way of achieving such levels of cooperation without honest willingness to share everything: equipment, key personnel and commercial information, clinical data, and so on.

But the sector's integration efforts, from the beginning, went beyond the idea of promoting cooperation within and among commercial companies alone. The inclusion of research organizations, universities, the whole health system, and government regulatory authorities has also played a crucial role. These efforts provide the foundation of the Cuban experience and are consistent with one of the fundamentals of Pharma 3.0, namely, to promote the capacity of a diverse set of stakeholders to be open and learn by connecting diverse datasets that allow the creation of common pools of information.

THE ROLE OF REGULATORS

The role of the regulator within the industry is one of the key aspects of broader integration efforts. For example, the issue of pooling data raises the question about standards, whose absence undermines the ability to collectively analyze the shared information. This calls attention, as the Pharma 3.0 paradigm acknowledges, to the need to engage regulators in the making of regulatory regimes that allow different assets and insights to be gathered in real time through more flexible approaches.

That means that stakeholders and regulators need to work together. This has been the case with Cuba's regulatory bodies, which operate under the authority of the health system and are responsible for overseeing drug registration, manufacturing, and clinical trials. Working in an environment of communication and transparency with regulators has helped align interests and common values in the development of data standards and has also enhanced public trust.

Cuban health ideology is based on the fundamental principle that healthcare is a right for all citizens and a responsibility for the state. When something goes wrong, nobody fares well, so there is a strong incentive among all stakeholders to make it work. The result is a complex network of organizations created by the state, of which the biotechnology industry has become a consubstantial element.

Part 2 of this article will appear in our June issue.

ANDRÉS CÁRDENAS-O'FARRILL is a Cuban economist whose research focuses on innovation and economic development. He has a Ph.D. in economics from the University of Bremen, Germany, and is also an associate researcher to the Academic-Industry Research Network (theAIRnet) based in Boston.

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Lessons In Leadership: "SKILL"

ARTHUR CARMAZZI

ARTHUR CARMAZZI is ranked as one of the world's top-10 thought leaders in leadership. He is a best-selling author, international speaker/trainer, and founder of the Directive Communication Organizational Development Psychology.

There are those who would have you believe that leadership is a set of skills, a specific recipe that one can follow and apply to inspire others to achieve greatness. Yet this magic formula that is considered the holy grail of productivity, management, and motivation seems consistently elusive. Yet multiple statistics indicate that training and human capital development does considerably and positively affect an organization's bottom line.

So if training works, why does leadership training often fail to improve a manager's ability to lead (also a statistic)? Where is the discrepancy between training success and leadership development?

The myth begins with the idea that competencies are directly related to specific skills. And that "skill" is a set of rules and actions — "Do this, get that." Since much of the leadership theory comes from either experience or a statistical analysis of successful leaders, herein lies the problem!

SPECIFIC SKILLS DO NOT EQUAL LEADERSHIP COMPETENCY

In 2013 we did a research study at DCI with a 70 company sample of poor, average, good, and great leaders. Our findings indicated that the only consistency among "great" leaders was an awareness of self and how they were affecting the people around them. Those who were considered "poor" leaders lacked that awareness.

A GREAT LEADER IS NOT CONFINED TO A SET OF ACTIONS THAT CAN BE COPIED

Another DCI study showed when individuals tried to emulate specific leadership models, 47 percent appeared inauthentic, and their leadership effectiveness varied from up to 8 percent less effective to marginally improved based on peer evaluations over one month.

APPLYING STANDARD LEADERSHIP MODELS IS NOT AN EFFECTIVE WAY TO DEVELOP LEADERS

Communication is a foundational skill for successful leadership, but each person has and applies different skill sets in different ways.

THE SOLUTION:

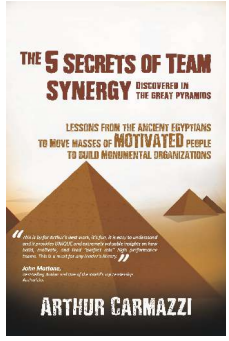
Each potential leader must meticulously develop their own personalized ideal leadership identity by discovering who they are at their best in different environments (e.g., at home, with friends). Next, potential leaders must reinforce and practice this leadership identity until it becomes natural in all environments.

NO CHANGE REQUIRED

When a potential leader is aware of how and when to access their better self — and see the results in real time — they become more effective.

WHAT TO DO NOW

We should stop training leadership skills and focus on a leadership experience that supports an ideal leadership identity. Create a constant feedback system for potential leaders and implement on-site coaching to have real-time awareness of actions. Finally, model personal successes and applicable role model successes that are congruent with potential leaders' current unrefined leadership characteristics.



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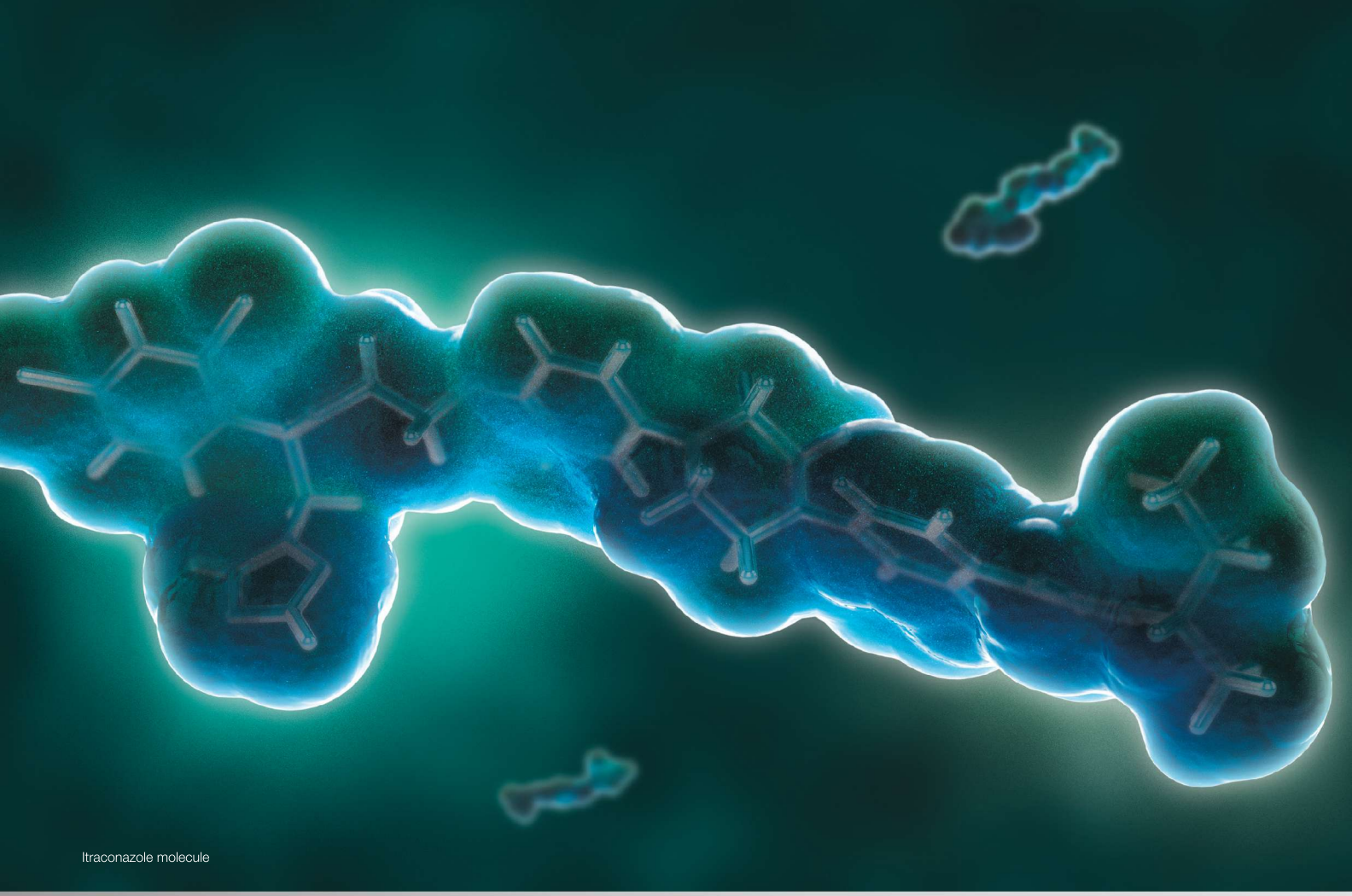

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