THE TAO OF R&D

Was last summer's conflict between Valeant and Allergan emblematic of a new era of innovation-killing corporate consumption, the last gasp of an old age, or something else entirely?

BY JAMES INCOLLINGO, MA, CONTRIBUTING EDITOR

Amid the commotion of the "bitterest takeover battle Wall Street has seen in years",[1] many observers feared that the traditional way of research and development (R&D)—one built on effort, expertise, and enormous capital investment sustained over time—was dead. A new, unsettling model of drug development by aggressive acquisition was threatening to devour the seed-corn of innovation and send thousands of R&D career professionals scrambling for new jobs. Most people cast Valeant as the villain and Allergan as the damsel in distress. Contrarians saw Valeant as the hard-nosed profit-seeker and Allergan as the money-wasting dinosaur.

In *CRST*'s July 2014 edition, then-Chief Medical Editor Eric Donnenfeld, MD, provided a thumbnail sketch of each company. He noted that they "could not be more different. Allergan invests a billion dollars each year in internal [R&D], and it is a longtime supporter of ophthalmology. Valeant is an upstart that takes over companies and slashes their research budgets." Dr. Donnenfeld admitted having initial concerns about the deal. He wrote that, upon "hearing of Valeant's bid and its predicted slashing of Allergan's R&D budget, the first thought of many ophthalmologists, including myself, was that patients and the field of ophthalmology would suffer."[2]

Others were more angry than concerned. In a contemporaneous piece, industry analyst Daniel R. Hoffman, PhD, observed that many "people in pharma and even some investment analysts came around to expressing their contempt for Valeant's entire business model and its effort to sacrifice a successfully operating pharma company [Allergan] to a pattern of destructive, short-term greed."[3]

Reactions got worse. Some in the business press raised the specter of a drug makers' apocalypse: "Valeant Pharmaceuticals is trying to acquire Allergan. ... The tactics it's using to do so might end up killing the pharmaceutical industry."[4]

Many people with careers at stake felt like Dr. Hoffman: "Allergan has done what good pharmas are supposed to do while maintaining a commendable, net operating margin of approximately 30%. If a pharma company that does good work and turns a handsome profit can get swallowed in the destructive maw of finance, then the industry's very existence as a sustainable venture comes into doubt."[3]

Allergan happily merged with Actavis last autumn, largely as a result of and ultimately thwarting Valeant's takeover attempt. Learning some lessons and still in good corporate health, Valeant moved on to greener pastures. The lawsuits between them have begun to be dropped, and the industry itself was not annihilated.

A hostile takeover attempt involving two iconic organizations can generate much controversy and even more commentary, as shown by Allergan and Valeant. Concerns, both sober and shrill, were voiced across the industry press and general media, but perhaps because the threatened takeover did not happen, the feared worst-case scenarios did not come to be. Health care providers who witnessed the noncatastrophe are left to sift through the facts and opinions to determine the context, meaning, and implications for their own careers, patients, and practices. There is much to consider, and in hindsight, the competing R&D mindsets—invest versus extract—seem less like competitors and more like two halves of a whole.

IT DID NOT HAPPEN OVERNIGHT

A staple of corporate maneuvering since the dawn of joint stock companies hundreds of years ago, mergers and acquisitions (M&A) have been running at a fever pitch in the pharmaceutical industry for decades. Between 1980 and 2010, the number of major drug makers declined from 34 to seven owing to M&A.[5]

Consolidation among generics makers specifically has taken a similar course, with 27 makers whittled down to 11 over the past 6 years. Most recent is an announcement that Teva Pharmaceutical Industries will buy Allergan's generic drug unit. As the number of competitors dwindles, concerns are growing that the matter may draw the attention of regulatory authorities charged with antitrust law enforcement.[6]

Although the downstream effects of M&A activity are not always positive for the acquired or the acquirer, the approach has long been seen as a way to gain valuable products and expertise, access to new markets, and cost savings from economies of scale as well as, occasionally, the chance to eliminate competitors by absorption. With

the regulatory burden on drug development at an all-time high, the number of drug approvals down compared with historical rates, fast-approaching patent cliffs for many drugs, and new competition from Europe, Asia, and South America, it is no wonder why the flurry of M&A has occurred.

Regulatory obligations alone can make it difficult for even well-run companies to stay competitive, and some feel that authorities deserved significant blame last summer for Valeant's voraciousness and Allergan's vulnerability. "If Valeant takes over Allergan," wrote Dr. Donnenfeld at the time, "I will blame in part the FDA for forcing pharmaceutical companies to devote an inordinate amount of their resources to research for an approval process that could be more expeditious."[2] So far this year, the dollar value of pharmaceutical deals is up 94% over the same period in 2014.[7] As a widespread ongoing trend, however, M&A mania is naturally self-limiting. In a conversation with *The Wall Street Journal* last summer, former Teva CEO Jeremy Levin explained the problem: "Valeant will eventually run out of things to buy and once it does, it faces the problem of how does it keep on the trajectory. A company without R&D short-term and mid-term can be viable, but [not] long-term."[3] Even with the M&A rate at its current clip, evidence is mounting that the train ride of feverish deals may be about to lose steam, because the effort is no longer panning out as well. In the year since Valeant's bid for Allergan, 12 public offers have been made for US-headquartered companies, but only two resulted in completed deals. That is a lot of work for not much return.[8]

Although the incentives driving increased M&A remain, the returns may be in for a nosedive. If that happens, where will companies turn for needed products, services, and expertise? The answer is probably not the traditional in-house model of R&D. Many companies are already experimenting with features of a new paradigm: partnership and collaboration.

According to longtime industry watcher, R&D professional, and CEO of the Pennsylvania Drug Discovery Institute Dennis Gross, PhD, "You're going to see more of this partnering, and it's going to be small companies and major research universities partnering with big pharma and midsized pharmaceutical companies to try to bring drugs up more rapidly, and try to transfer some of that bench

INDUSTRY ROUNDUP

To determine if attitudes and actions toward research and development are evolving as predicted, *CRST* interviewed executives from a roughly representative sample of eye care product manufacturers. Questions dealt with their policies, opinions, hopes, and concerns, as the industry responds in new ways to economic and social forces, current and looming.

ELEVEN BIOTHERAPEUTICS

Smack in the middle of the Boston-area biotechnology hotbed, Eleven Biotherapeutics was started less than a decade ago to exploit an innovative AMP-Rx protein engineering technology. With a market capitalization of just $68 million, the company represents the newer, smaller, biotech startup operations that are frequent targets of larger companies seeking acquisitions. Eleven's dry eye drug EBI-005, a targeted, dual-action therapeutic for dry eye disease and allergic conjunctivitis, failed to meet its phase 3 primary endpoints. Upon the announcement on May 18, the company suffered a 70% drop in its share price, from which it has yet to fully recover. Such volatility can be a factor with startups, as opposed to older firms with tested products, simply because the former are new entities with uncertain products, so investors are more likely to panic at any bad news. Likewise, some have warned of a "biotech bubble," which may be bulging.[1]

In a conversation with *CRST* prior to the release of the EBI-005 results, Dr. Celniker spoke about her company's commitment to R&D [research and development] and how it might shape potential partners: "We really decided that what was needed in ophthalmology was innovation, because so many companies simply repurpose existing drugs and sell them, as opposed to really keeping an understanding of the biology behind the diseases and then developing candidate drugs for those. Our whole premise is to be very innovative in ophthalmology, so when it comes to companies like a Valeant or Allergan or other ophthalmology companies, we would not necessarily want to be in partnership or purchased by a company that was going to squelch our innovation. We think that the unmet needs in ophthalmology [are] so significant that the patients deserve companies that will innovate in their area. That doesn't mean that we wouldn't collaborate with other kinds of companies that might not have a big innovation infrastructure, but they appreciate it to the point they will partner with companies in order to maintain their ability to innovate without necessarily investing in it with their own infrastructure. Our hope would be to continue to innovate for the benefit of patients."

With regard to partnering, collaboration, and the democratization of pharmaceutical manufacturing, Eleven Biotherapeutics is fully on board. Dr. Celniker, a molecular biologist with managerial experience at a range of other pharmaceutical firms, is particularly proud of the expertise within her company: "The way we approach things is to bring in the world's experts and authorities on a certain subject matter and then, instead of a bricks-and-mortar building with a lot of people working, which is a drag for the company, we take the deep subject matter expertise of our leadership group, and we allow

knowledge into the clinical a bit more rapidly so [that] we have the drugs we need in the future."

Trends aside, if every drug and device maker of sufficient size engages in M&A eventually, why was Valeant the subject of ire?

STYLE VERSUS SUBSTANCE

Valeant is not a villain but rather a group of motivated people with certain skills and resources competing for success in the pharmaceutical industry. Those who have lost jobs to Valeant's acquisition activity may not agree, but just about every pharmaceutical company of medium to large size has grown, at least in part, by acquisition. When executed well, this strategy can benefit all involved, even consumers. Valeant has been at the leading edge of this growth strategy in the pharmaceutical business. However, the criticism, anger, and vitriol directed at the company seem to have as much or more to do with shortcomings in its public relations style as they do with its strategic maneuvers. Pharmaceutical firms have been devouring each other for decades, but approaches to acquisition differ, as do the reputations that attach thereto.

Behind the scenes, however, the bottom line is often the same. According to Eleven Biotherapeutics' CEO Abbie Celniker, PhD, Valeant is just upfront about it: "Some companies try to pretend that they're not like that, but in truth, they grow through acquisition. While they may do very little research or development, they give a façade that they do. In reality, they operate very similarly to Valeant."

Prof. Gross has been studying, teaching, and working in drug R&D worldwide since the late 1970s. In a conversation with *CRST*, he agreed that *acquisition* is not a dirty word: "There are a lot of companies that have grown by acquisition, even Sanofi for many years in the French market. Sometimes, you do it to fill a niche. Valeant sort of has a reputation for going after other companies, and they do grow by acquisition, sometimes to fill gaps in their portfolio. They're also always trying to address this patent cliff by acquiring products that have a slightly longer patent life so [that] they have a longer runway to be able to bridge to the next new marketable drug. But, there's always the worry that a lot of people will be 'streeted' in the process. So, it is sort of a yin-yang in that they grow by acquisition them to go out and design the most effective way to get things done through contract research organizations and contract manufacturing organizations. That's worked very efficiently for us, but the key to doing that successfully is having very, very experienced people as part of the company."

Although Dr. Celniker is confident Eleven Biotherapeutics can market its medicines domestically all on its own, the company is interested in strategic partnerships that would enable it to commercialize its molecules in other countries: "One of the key things we look for are the kinds of companies that could be commercial partners with us outside of the [United States] but still maintain a philosophical synergy with the way we think about things," she said.

Her view of the regulatory burden is that it seems to be lying less heavily these days. "I think the regulatory authorities are collaborating a lot more with biotech companies as well as bigger pharmaceutical companies, and the real key is to have conversations with those regulatory authorities, early and often," Dr. Celniker commented. "What's really important from our perspective is that the regulators are thinking about the unmet needs of the patient, and that they are spending the time thinking about how these innovative products can get to the patients as quickly as possible." Referring to Shire's garnering of an expedited review for lifitegrast, she added, "I think we've recently seen some movement in this area in ophthalmology."

With several drugs in clinical trials right now, Dr. Celniker unsurprisingly says that the biggest challenge facing Eleven Biotherapeutics is "getting those trials up and running and making sure that the company is financed in a way that we can take advantage of things that we observe in each of our clinical trials."

It is the excitement of innovating and creative partnering in a growing market, however, that captivates Dr. Celniker's attention: "Based on our aging population and some of the ophthalmic complications that come with age and other diseases, we really think it's important that there is continued innovation in this area, and we think there's a nice balance between what the small biotech companies can do to create incredible value for patients by innovating in that space and leveraging the infrastructure and size of the larger companies. We've seen this work in many other therapeutic areas very durably for 30+ years now of the biotech industry, so we're hopeful that that kind of sustainable biotech innovation in ophthalmology, synergistically collaborating with bigger pharmaceutical companies, will continue because that's what's going to provide the best benefit for patients both near term and long term."

SHIRE

Founded in 1986 and with a current market cap near $46 billion, Shire is a midsized, middle-aged firm that targets early-stage candidates for acquisition while investing heavily in its own R&D. Located in Dublin, Ireland, for tax purposes, the firm's US operational headquarters are in Lexington, Massachusetts.

In an interview with *CRST*, Shire's Ophthalmics Business Unit Head Robert Dempsey addressed the company's orientation toward R&D. He explained, "We're taking an old-fashioned, not as popular approach to driving growth. We see ourselves as a biotech company first and foremost, and we invest significantly into R&D. At the same time, we look to bring in opportunities

but that also allows them to move into areas where they probably didn't have the core competency to be in, and this lets them branch out and create a better portfolio for their company."

"There are two sides to it," Prof. Gross added, "but Valeant always seems to get reported as a very aggressive type of company, vocal in the press about whom they intend to go after and buy. Now, there are plusses and minuses to doing that internally, because it's demoralizing to people when they realize that they're only being bought for their patent portfolio and really not their expertise. They wonder what's going to happen to them. With the thousands of people in pharma that have been let go in the past decade or so, it becomes a little disconcerting when you become a takeover target like that. Honestly, though, all takeovers are hostile takeovers. There's no such thing as a friendly takeover, and that's something we have to keep in mind."

Headquartered in Canada, Valeant has been unapologetic about its aggressive approach to "inorganic" R&D and to potential M&A targets. Years of this policy seem to have culminated in the Allergan takeover attempt, which unleashed a tsunami of criticism from across the industry and beyond, particularly from those who felt like someone was chipping away at the foundation on which their professional worldview was built. Notably absent from much of the spleen-venting were Valeant's shareholders, perhaps because they have seen the company's stock price rise 1,000% in the 4 years following Michael Pearson's 2008 ascendance to CEO.[9]

Nevertheless, even Mr. Pearson paused for self-reflection in the aftermath of the firestorm. Speaking with the *Financial Times* in January, the Valeant CEO admitted some mistakes in the Allergan affair. He said he regretted not taking the threat from Actavis more seriously and doing a "poor job" of communicating Valeant's feelings toward R&D, which allowed Allergan to define the company negatively.[10]

Today, the industry is left with a question: if Valeant is going to moderate its muscular tone, if the hostile takeover itself is losing support as a stand-alone R&D strategy, and if all the same pressures of pharmaceutical development and marketing remain in place, what will replace the drama of villain versus damsel, of extract versus invest?

INDUSTRY ROUNDUP (CONTINUED)

through [mergers and acquisitions] that fit within our overall strategy. I think the big difference between what a lot of the other companies are doing in this space and what we are doing is that we are probably betting on earlier assets."

In that vein, Shire recently purchased companies with drugs in early development for both retinopathy of prematurity and autosomal dominant retinitis pigmentosa, which will require a continuing R&D commitment to bring to market. According to Mr. Dempsey, Shire will take considered interest in later-stage opportunities as well. Shire's recent acquisition of Foresight Biotherapeutics is one such example. Through that acquisition, Shire gained the late-stage asset FST-100, an investigational compound for the treatment of infectious conjunctivitis. "We also purchased lifitegrast, a relatively late-stage phase 3 dry eye treatment program," he said. "Lifitegrast required and FST-100 will require further research and development. With lifitegrast, we've submitted an NDA [new drug application], which was accepted for priority review, and we're now waiting to hear back from the FDA by the PDUFA [Prescription Drug User Fee Act] date of October 25. In the meantime, we've embarked on a significant effort to communicate Shire's commitment to growing our business in ophthalmics."

Shire is also keen on the synergies that can occur by applying its own R&D experts to newly acquired prospects. This approach worked particularly well with lifitegrast, because Shire's "dedicated drug developers looked at the information on lifitegrast through a different lens than the company from which we acquired the compound. With that particular perspective, we were able to evaluate it and select a path that we hope will lead to a successful approval of lifitegrast," Mr. Dempsey explained.

When it comes to R&D business models, Shire takes a hybrid approach, but Mr. Dempsey was quick to "emphasize that, while the hybrid includes late-stage opportunities such as lifitegrast, we're placing bets on early opportunities that address unmet needs yet are very innovative assets, ideally new chemical entities. Therapeutics that focus on unmet needs [are] really the core of what Shire wants to do from an ophthalmic standpoint." That is a space Shire is vocal about occupying. According to Mr. Dempsey, the company is "in the process of building out a medical affairs team, an R&D team, and now with the lifitegrast NDA accepted for a priority review, a commercial team. With these three pillars of the organization in place, along with the investment the company is making, we want to show the eye care community that we are here to stay and we intend to expand. We're building a portfolio of products, we're building a pipeline, and we are high on the list when companies with novel eye treatments are ready to look into partnerships."

As far as the company's presence in the industry and with the doctors and patients it serves, Mr. Dempsey wants them to know that Shire is clearly "investing in the R&D function. We are actively recruiting and retaining talent. Shire is a biotech company with a robust pipeline in ophthalmology and across many disease states that is as good as it's ever been. We have made some significant investments in business development personnel to bring in early to midstage opportunities, to put them under our R&D umbrella and bring them to market. It's somewhat old-school, but we believe it's still a viable strategy

THE NEW NORMAL: LET'S COLLABORATE

Although M&A remain popular options for gaining valuable product lines and desirable expertise, a softer approach may be coming to the fore. Collaboration, connection, and partnering for mutual profit are emerging as popular responses to the economic demands on today's pharmaceutical industry. This shift was probably inevitable, owing to a shrinking pool of attractive takeover candidates, but it may also be an evolved reaction to the human toll that aggressive, relentless M&A can exact on even the most dedicated workers, regardless of their positions on the company organization chart. Change may be good, but chronic instability chafes over the long term.

In order to avoid both acquisition starvation and mass employee burnout, forward-thinking companies are re-exploring the benefits of flexibility and nimbleness, and they are narrowing their focus to play to their own strengths. As a result, networks are developing among startup biotechnology companies, big manufacturers, contract research organizations, universities, and others so that each can offer what it does best (eg, primary research, phase trials, regulatory approvals, manufacturing, distribution, accounting, sales) and can outsource those business functions where it lacks expertise.

Prof. Gross recalls an industry during the 1970s and 80s, when "everybody was focused on doing everything. We had huge labs, we had multinational laboratories, we had facilities everywhere, a global laboratory, and we've come to the realization for a lot of companies that you can't do that anymore." Today, the climate is different, and "that's why a lot of companies have started hedging their bets. They're not building as many labs as they used to overseas, but they're doing a lot of work overseas, and they're doing a lot of collaborative projects with universities. They're trying to set up these centers of excellence like Pfizer is doing, where Pfizer scientists work at the university, and sometimes the university scientists work at the industrial scientists' site. They're learning the mindset of how you approach problem-solving, how do you approach risk management, and how you mitigate the risk when developing a project that takes 12 years and $2 billion."

Prof. Gross added, "People talk about 'lean manufacturing,' but one of the things we need to look at is lean research and this concept of the virtual pharmaceutical

for a biotech company to identify the right opportunities, invest in R&D, and take them to market."

ALCON

Acquired in 2011, Alcon is a wholly owned subsidiary and the second largest division of Novartis. Novartis' market capitalization of $263 billion dwarfs the other manufacturers on this list by a factor of more than two. Headquartered in Fort Worth, Texas, and founded in 1945, Alcon has grown into a major ophthalmic drug and device maker.

In a statement provided to *CRST*, Peter C. Richardson, BMedSci, BMBS, MRCP, chief medical officer, addressed Alcon's exceptional and ongoing R&D commitment: "Alcon invests more than USD 1 billion annually in R&D, a commitment that is unmatched in the private sector. In addition, we have a global team of more than 2,000 highly skilled individuals dedicated to R&D. As a result, we have a comprehensive portfolio of best-in-class products and devices."

Alcon's strategic approach is to seek a balance between innovative R&D, strategic acquisitions, in-licensing, and partnerships with third-party organizations. The company is currently working on developing next-generation treatments for wet age-related macular degeneration [AMD], which Dr. Richardson hopes will "help us expand our presence in medical retina, one of the fastest-growing segments in eye care."

Alcon recently signed an agreement with Google[x], which Dr. Richardson pointed to as "a way that we are building our pipeline through partnerships in addition to pure R&D. Their 'smart lens' technology has the potential to transform eye care by helping people with presbyopia by restoring the eye's natural autofocus on near objects in the form of an accommodative contact lens or IOL."

He added, "We've recently launched the Verifeye+ upgrade to the ORA System. ORA is an intraoperative guidance system that helps lead to enhanced cataract outcomes, particularly among astigmatic patients. This stemmed from the acquisition of WaveTec Vision, developer of the first technology of this kind within the cataract market. With the acquisitions of LenSx, Endure Medical Systems (LuxOR), and WaveTec (ORA), we added critical components to the Alcon Cataract Refractive Suite."

Dr. Richardson said the outlook for the eye care industry is strong and that Alcon is uniquely positioned to thrive in the coming years: "The aging population is creating an expanding pool of patients and increased demand for quality eye care. Although a treatable condition, age-related cataracts affect close to 20 million people, the leading cause of blindness. Twenty-five million people currently suffer from AMD. Twenty-seven million people suffer from glaucoma, one of the leading causes of preventable blindness. At the same time, emerging markets are demanding greater access to quality care." As far as Alcon is concerned, it is a good time to be in the ophthalmic pharmaceutical business.

VALEANT/BAUSCH + LOMB

Founded in 1960, Valeant gained significant attention by acting like a big pharmaceutical company when it was still fairly small, largely under the direction of current CEO Michael Pearson. They

company: if it's not something that you really do well, or need to do on a daily basis, a lot of that is going to be outsourced or off-shored, or lead to a partnering relationship. Contract Research Organizations are a good example of that; we've been outsourcing to them since the 1970s for things like helping with [investigational new drug applications] NDAs. We've gone from being simply a contracting relationship now to a partnering relationship."

Ripe with potential, this new age of collaboration could lead to untold efficiencies and a blizzard of innovation, and the range of players in ophthalmic R&D are already leaning in.

OPHTHALMIC PHARMA'S APPROACH TO R&D: GETTING THE BALANCE RIGHT

It might be evidence of the industry's blossoming commitment to nimbleness, but nearly every pharma today wants to be perceived as very R&D friendly. Although none has sworn off M&A attempts, even Valeant has learned to speak in more measured tones about what many strongly believe to be the beating heart of the whole pharmaceutical enterprise: top-notch research driving drug development that serves the needs of patients.

A capitalist economic system insists upon profits and shareholder returns, and some coming from finance and economics backgrounds may celebrate that as an end in itself. Typical microbiologists, organic chemists, or research ophthalmologists, however, want something more—they tend to get the most joy from discovering, developing, and debuting a drug, device, or technique that matters in the lives of real people. Accounting for that desire, fostering it, and channeling it appropriately are all becoming new imperatives, right alongside the push to find efficiencies through smart cost-cutting, partnerships, and collaborations.

In a report last year on the formulation of a model for success in pharmaceutical R&D, research scholar Hyunju Rachel Kim predicted that success in the industry will depend on accepting a new model of development in which a "firm's R&D strategies and R&D managerial capabilities comprise the key constructs that bring about efficient innovation. Outsourcing, collaboration, and offshoring R&D strategies are understood as significant ways toward efficient innovation. R&D managerial capabilities are defined by managerial openness and strategic

acquired Bausch + Lomb in 2013. Now, with a market capitalization of $79 billion and with the 2014 Allergan takeover attempt receding in the distance, the Quebec-based firm is eager to communicate why its R&D approach is valid, even optimal, and based on outputs rather than inputs.

In a statement provided by Valeant, Ari Kellen, MD, head of US Eye Health for Bausch + Lomb, detailed the principles guiding their R&D strategy going forward: "We at Valeant and Bausch + Lomb are fully committed to supporting the eye care community and serving the needs of the doctors and patients who rely on our portfolio of products. Bausch + Lomb's mission, helping people see better to live better, is being realized under the leadership of Valeant Pharmaceuticals. Since the acquisition, Bausch + Lomb has launched approximately 15 new products into the US market, helping to fulfill unmet needs in optometry and ophthalmology. We are excited to provide a compelling, comprehensive portfolio of eye health solutions around the world, and have many promising development programs across our surgical, pharmaceutical, contact lens and over-the-counter portfolio. These include our Spectrus surgical navigation system, which was previewed at the American Society of Cataract & Refractive Surgery 2015 meeting, Vitesse, a revolutionary new technology for vitrectomy, and Vesneo [latanoprostene bunod ophthalmic solution 0.024%], which if approved, will be the first nitric oxide-donating compound for patients with open-angle glaucoma or ocular hypertension."

Essentially, Valeant is standing the traditional in-house R&D method on its head by focusing its internal resources on development, while partnering with academic centers, startups or doctors to source innovation. The company seeks to deliver that innovation by applying its unique approach to enhance efficiencies in development processes to quickly bring advances to market.

According to Dr. Kellen, "Each development project is evaluated on the basis of its merits, irrespective of whether the idea was internally or externally generated, or whether it fits into a preconceived budget for R&D. Our R&D spend is thus adjusted based on the promise of our programs as well as whether it is meaningful innovation that fulfills the needs of our customers and their patients. In fact, Bausch + Lomb has more R&D projects in its pipeline today than ever before."

Dr. Kellen added that, because "no big pharma company can have full research capabilities in every area," Valeant believes "the future of ophthalmic clinical development is to take a newer, more nimble approach to R&D, where large companies create partnerships and alliances with universities, physician groups, and startups. We're continuously working to identify new enhancements and improvements that will support our doctors and the patients they serve, and many times this occurs in direct partnership with those who are using our products. By regularly communicating with our customers and the FDA, we're helping to address the ever evolving needs of the eye care community, which can be seen in our surgical business through new indications and software and hardware upgrades."

Valeant/Bausch + Lomb is intent on being the industry leader in bringing innovative products to market—among them, the internally developed Ultra and Biotrue ONEday contact lenses, Stellaris PC Vision Enhancement System upgrades, and PeroxiClear hydrogen peroxide solution; the licensed

cognition; managerial openness consists of the openness to new technology, openness to networking, and openness to information sharing."[14] Clearly, some in the pharmaceutical industry were ahead of Ms. Kim's curve.

THE WAY OF R&D

Instead of the winner-take-all view archetypal of the Western world, an Eastern perspective on the ways of R&D reveals an oscillating cycle of opposing yet complementary orientations, endlessly seeking equilibrium. This concept is embodied by the familiar yin-yang symbol of the Taoists. To them, it represents the false duality of all things in apparent opposition (life versus death, invest versus extract, Valeant versus Allergan), which masks their true nature as inseparable components of a larger whole. It may prove fruitful for everyone with an interest in pharmaceutical development to remember the yin-yang—the endless back-and-forth—the next time a ballyhooed catastrophe seems poised to end it all.

R&D professionals, however, may take comfort in having survived the dispute that threatened to "destroy the industry as we know it."[15] Instead of homelessness and destitution, they are likely facing quite bright futures in their chosen careers. Prof. Gross is certain he made the right choice: "I started out being a professor in a university, and I wound up going into the pharmaceutical industry, because what I enjoyed was applied science. From that standpoint, biopharma is probably one of the best places for someone who is truly interested in applied science. The resources are there, the depth of knowledge is there, and just working in a global laboratory is an exciting experience. I loved every minute of that work because of the people I worked with and the countries I worked in."

As for practicing ophthalmologists, Dr. Donnenfeld told *CRST* in an interview that hopes his colleagues will embrace their roles as "the voice of our patients, and it is our obligation to push the status quo, to encourage innovation, and to develop new treatment options for patients. We can't sit silently in the background while issues that are important to patients are resolved. We have to take a more proactive political voice in helping to develop new technologies and pharmaceuticals."

Regarding Valeant and Allergan, he sees more similarity than difference, like two paths up the same mountain:

technologies Soothe XP-Xtra Protection eye drops and enVista IOL; and the externally developed Sjö diagnostic test for Sjögren syndrome and Prolensa (bromfenac ophthalmic solution) 0.07%. Valeant believes their track record of new product launches across eye health and dermatology confirms the success of their strategy and R&D philosophy.

Other observers may feel differently, but after a year to think about it, Eric Donnenfeld, MD, has developed some not-quite-grudging respect. In an interview with *CRST*, he said, "I'm impressed by [Bausch + Lomb]/Valeant's commitment to innovation by acquisition, and while it's a completely different business model—and yet unproven over the long run—I am involved with several different startup companies that are having very serious talks with Valeant about their technologies, and I'm not willing to say that one model is better than another. It's going to have to play itself out. It's not the model that is important; it's actually how the model is implemented. Implementation is the key to the success of both Valeant and Allergan, and either model will work very effectively, as long as you have the leadership dedicated to achieving the end result that they're looking for. Honestly, I think that Valeant could have done a good job with Allergan. On the other hand, if it's not broken, don't fix it."

Lest anyone think Valeant has mellowed too much, the company demonstrated its nimble enthusiasm once again last August, by moving with relative lighting speed to snap up the women's libido boosting drug maker Sprout Pharmaceuticals for a cool billion dollars, a mere 48 hours after Sprout's drug Addyi earned approval from the FDA.

ALLERGAN

With a presence in about 100 countries and a market cap of $119 billion, Allergan is a global pharmaceutical company focusing on branded, generic, and over-the-counter medicines and biologic products. The company's global headquarters are in Dublin, Ireland, and its administrative headquarters are in Parsippany, New Jersey.

No more a damsel in distress than Valeant was a villain, Allergan merged with Actavis last November, stopping cold Valeant's takeover bid. After the storm, stress, and worry about the death of R&D over the previous months, the deal met with nearly universal approval. Dr. Donnenfeld believes the company "is reinvigorated by the merger with Actavis, and that Brent Saunders is going to provide a spark of leadership that's going to make Allergan an even more vibrant company. In speaking with people there, I've noticed a more dedicated emphasis on ophthalmology and on coming back into ophthalmology in a more significant way. For many years, Allergan was the leader in ophthalmic pharmaceuticals, and over the last several years, there's been less emphasis on anterior segment surgery than there was in the past. But now, I'm seeing a new dedication that is exciting for me as an ophthalmologist, and I think it's going to be good for ophthalmologists across the board."

Interestingly, Allergan CEO Brent Saunders was with Bausch + Lomb during its takeover by Valeant in 2013. It is intriguing to speculate whether that gave him special insight into how to stifle Valeant's 2014 interest in Allergan.

For a current take on the company's approach to R&D, *CRST* spoke with David Nicholson, head of branded R&D at Allergan.

"Great leaders take companies and make them better, and there are a lot of different ways of going about doing that. Different leaders have different strengths, and Valeant's strength is clearly acquisition, and Allergan's strength is clearly development. At the end of the day, we hope both of them are successful."

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INDUSTRY ROUNDUP (CONTINUED)

"I think the very fact that Actavis has adopted the Allergan name speaks volumes about how delighted we are to bring these two incredibly strong organizations together," he remarked. Dr. Nicholson, who holds a PhD in pharmacology, has spent his career in R&D and seems utterly without doubt that he will continue to pursue his traditional passion within the new, bigger Allergan: "I wouldn't have joined Actavis if I wasn't convinced it was truly committed to the normative R&D model. Obviously, I'm very excited to bring together the strong R&D presence of Actavis with Allergan's more than 60-year history of R&D within ophthalmology, dermatology, and devices. Bringing Allergan together with Actavis' particular expertise in CNS [central nervous system], women's health, infectious disease, and some gastrointestinal disorders is a natural. At Allergan, we love R&D, and we're heavily committed to it. We have a very specific model of R&D, but nevertheless, R&D and innovation are the core of our company, they are the foundation of our company, and they are something that we have no intention of stepping away from."

Following their "growth pharma" model, Allergan under Mr. Saunders should not deviate from its well-worn R&D pathway and, not surprisingly, hopes to grow its R&D budget up to 10%. "Many large pharmaceutical companies have struggled in recent years to grow their top line of drugs," said Dr. Nicholson. He added, "I believe that, if a company is really going to be growth pharma, if it is going to be able to grow at that rate sustainably, you really need to have your own R&D."

R&D requires people, and Allergan is committed to keeping them present and busy. Dr. Nicholson said the biggest challenge is bringing people together and making sure they come to work at this new organization with a positive attitude: "I say this all the time at town hall meetings. We've got incredibly talented scientists, and the important thing is they get up in the morning happy to go to work with a smile on their face and continue to drive their projects. By doing that, we can keep the momentum in the pipeline, continue to hit our milestones, and continue to launch projects. People who are motivated, who feel empowered, can drive projects which allow us to hit our milestones. Since the start of the new company, we have prioritized and motivated the pipeline, and we've made sure that people know their projects are continuing."

"In terms of ophthalmology, we have a strong pipeline with lower formulations of Restasis [cyclosporine] in late-phase development," Dr. Nicholson said. "We have a novel sustained-release formulation of bimatoprost to treat glaucoma in late-stage development. We are developing new tears for over-the-counter use. We are about to enter phase 3 with our DARPin project, which is a collaboration with Molecular Partners in Switzerland, as an emollient agent for the treatment of AMD and diabetic macular edema. So, we have a strong pipeline, we're driving it forward, and we are truly delighted to do so."

Dr. Nicholson continued, "I'd like to stress that the bold, new Allergan is in ophthalmology and we're in ophthalmology to stay. People should not think that, because of the merger, that the company is any less committed to ophthalmology. We are committed to develop drugs, one of the few companies heavily committed to that area, and we intend to remain so."

Asked about the Valeant takeover episode and what it means now to Allergan, Dr. Nicholson was more interested in facing the future, but he acknowledged that "it became possible for Allergan to merge with Actavis because of the approach by Valeant, and if that hadn't happened, perhaps Allergan and Actavis would never have merged." For Dr. Nicholson, other than opening the door to Actavis, last summer's uproar is old news. "We're bringing together two very strong people-based organizations, and it's the people in the organization who drive the pipeline. To me, that's the real story." ■

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