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JULY 2016

Seeking Solutions To Drug Pricing

Go inside our closed-door roundtable that included pharma, payer, and patient advocate executives seeking solutions to this volatile topic. p. 16

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What Is At The Heart Of Biopharma Backlash?

ROB WRIGHT Chief Editor

I'm dismayed by the ongoing negativity that dominates much of the mainstream media's coverage of our industry. I admit there are significant opportunities for improvement and that mistakes have been made, but what about solutions? Sure, I understand we are all wired to pay more attention to controversy and wrongdoings, but how much worse can it get? I mean in a few keystrokes anyone could probably find a number of polls and studies that show a rising sentiment against (i.e., unpopular) the pharma industry. I get it — the industry is seriously under fire, but I started to wonder about some of the *underlying* issues that have led to this current dilemma.

I came across an interesting 2014 *NY Times* article titled "The Rise of Anti-Capitalism" that posited something I feel is at the heart of the pharma industry backlash. According to the article, "The inherent dynamism of competitive markets is bringing costs so far down that many goods and services are becoming nearly free, abundant, and no longer subject to market forces."

In a free market society, the opportunity to make money creates competition, and noncollusive competition typically creates lower prices. Competition and lower prices are usually good for consumers — that is until the ability to make a reasonable profit gets squeezed to the point at which competition decides to leave the space. A good example of this concept is Merck's bladder cancer therapy, TICE BCG. Being 30 years old, the drug lost its patent exclusivity long ago but is still in short supply (Merck still makes it). So if other companies could make a reasonable profit in the manufacture and sale of BCG, in a free market wouldn't competition naturally enter to fill the void? If so, then why hasn't this happened? Of course my fear is that without some reasonable profits, pharma companies won't be able to invest in R&D for new drugs, and other existing therapeutics may soon be short in supply.

Another issue tarnishing biopharma's reputation is the industry's lack of price transparency. The industry's current WAC (wholesale acquisition cost) pricing scheme (see our April 2016 article on Suresh Kumar, EVP of external affairs for Sanofi) not only inhibits a patient's ability to determine how much they should be willing to pay for a drug but impedes biopharma from providing true drug price transparency. As a former drug rep we used to give away pens. I remember a doctor once asking me, "Why don't you stop giving away these pens and just lower your drug prices?" Unfortunately, such silver bullet type solutions applied to complex problems usually don't work. After all, you wouldn't prescribe a Band-Aid to a skin cancer patient, so why then do we take similar approaches in tackling today's current drug-pricing issues?

I believe that to move forward, we need to *truly* treat patients as partners and start living up to those proclamations of being "patient-centric." But how we do that, and all the other steps associated with a solution to the industry's current pricing and reputation woes, isn't going to be easy, and it's going to take a long time. (For more info, see the article on our recent pricing panel on p. 16.) The question is: Are we up for the challenge? L

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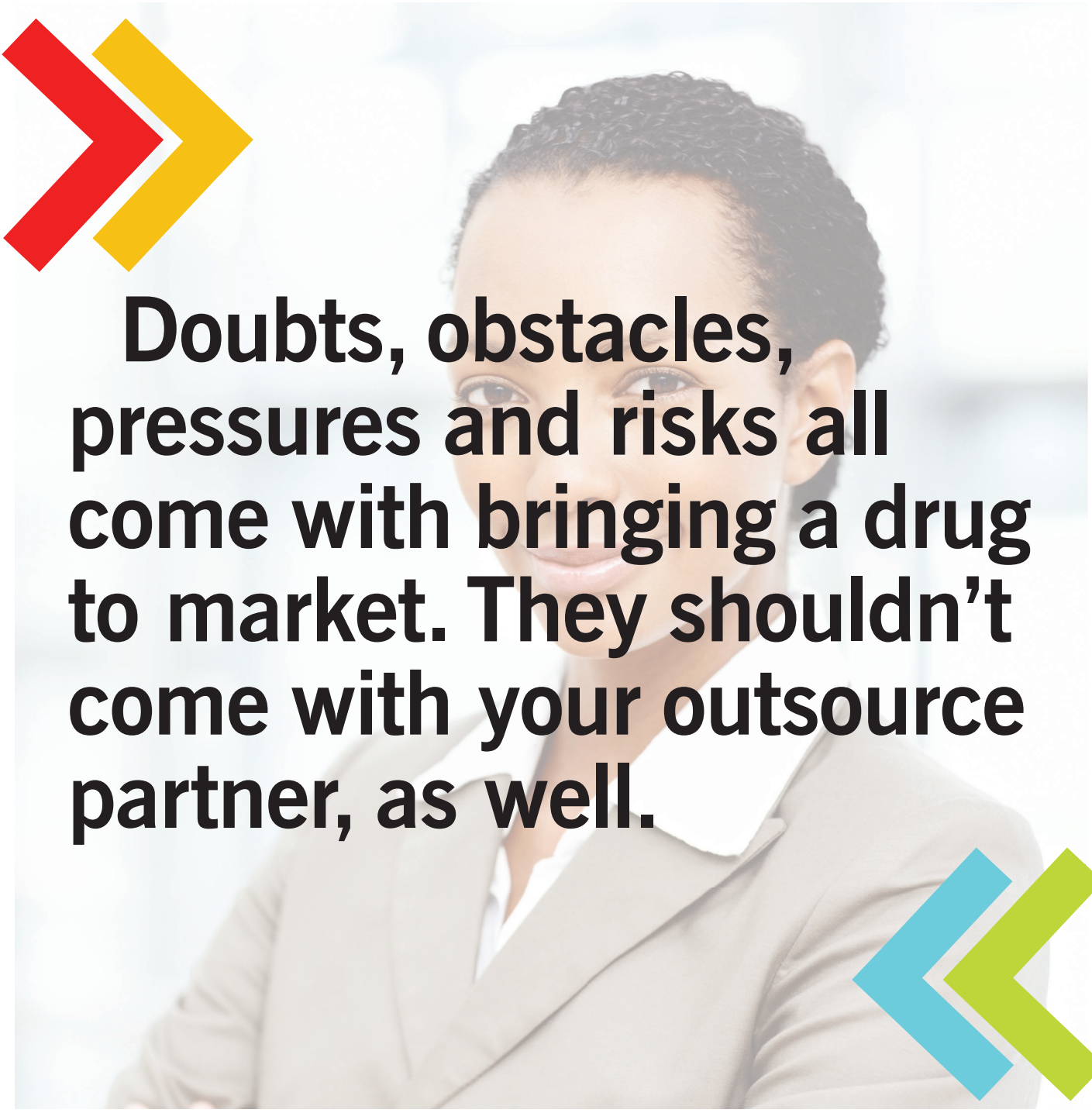

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Q There are rumors that the contract drug substance (DS) and drug product (DP) manufacturing capabilities past 2017 are fully booked, leaving the pipelines of bio to fend for themselves. Any validation to that?

A SOME OF MY SOURCES INDICATE THAT DS CAPACITY is largely consumed at the current time. Major biologics enterprises continue to expand internal capacity, which indicates the dwindling capacity at CMOs and the continued expectations of new biological products in the pipeline. The same does not appear to be true of DP capacity, as pricing for this entity remains competitive, indicating some excess capacity. Similarly, these assets are fungible across product types, and demand often can be shifted as volumes change. However, as many firms wait for confirmed demand and high line occupancy prior to investing in new lines, there are often periods of limited capacity while new capacity is added. It's possible that 2017 could be a year of short contract capacity for both DS and DP.

JIM ROBINSON
is the former VP for vaccine and biologics technical operations for Merck & Co.

Q Do you think the FDA Draft Guidance on metrics takes the industry in the right direction?

A THE INTENT OF THE COLLECTION OF INDUSTRY METRICS IS IN THE RIGHT DIRECTION. To date, the information the FDA gathers is limited to compliance data, which provides only a snapshot of the compliance level of a site and some indication of quality based on a limited set of surrogate measures. Having a collection of specific quality metrics can bridge the gap between snapshots and a more real-time depiction of the quality at a site. We will have greater clarity regarding what information will be used in determining potential inspection frequency and focus. Conversely, the FDA will have a more expansive data set to make well-supported, risk-based determinations, and subsequently allocate resources to sites of greatest risk to the patient. However, part of the "right direction" will require addressing the diversity of the industry and product landscape while still providing an effectiveness measurement of the metrics program itself.

JASON URBAN, PH.D.
is the senior director of global quality operations for Celgene Corporation.

Q Do you think the FDA Draft Guidance on metrics takes the industry in the right direction?

A THE CHALLENGE RESIDES IN FINDING THE RIGHT PREDICTIVE MEASURES that can best prevent problems for industry's constituents. We know it takes a battery of measures to understand the robustness of operations (e.g., quality management systems, processes, products, and facilities) to ensure fit-for-purpose. Good measures must also evolve as operations change and mature. If our goal is problem prevention, we need predictive measures that are specific to operations that allow us to proactively take action. A majority of the proposed metrics are *descriptive* (what has happened). These may be able to offer potential correlation to events after the fact. However, appropriate *predictive* robustness measures will increase the likelihood of problem prevention. Alternatively, let's consider establishing guidance for an internal measurement program (which could be tailored to the site/company), and make these subject to inspection.

CHARLENE BANARD
is the head of quality and technical operations at Shire.

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Administration's Response To Antibiotic Challenge Falls Far Short

JOHN McMANUS The McManus Group

Public health advocates have been sounding the alarm bell for years that current antibiotic treatments and the limited few in development cannot address the rising crisis of drug-resistant superbugs. According to the Centers for Disease Control and Prevention, we are at a crisis point, with more than two million Americans annually being treated for infections that are resistant to antibiotics and more than 23,000 dying in the U.S. as a result.

But the recent finding of a Pennsylvania woman with a superbug carrying the plasmid-transferred MCR-1 gene — previously discovered in Chinese animals in 2015 and seen as unstoppable — caught the nation's attention. MCR-1 is resistant to Colistin, an antibiotic of last resort, and its ability to jump from bacteria to bacteria can potentially result in widespread pan-resistant infections.

A key issue is proper stewardship of antibiotics — to ensure they are used judiciously and appropriately in order to slow the development of resistance. That's clearly going to be a challenge as China alone used 12,000 metric tons of Colistin in farm animals in 2015, and only this year did India begin to limit OTC sales of antibiotics. But even if we eliminated all use of antibiotics in animals and all unnecessary use in humans, we still are bound by a pathetic pipeline to combat what we're facing now.

Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, testified on this crisis at the House Energy & Commerce Committee on June 14: "The decline in antibacterial drug research and development in the private sector, at a time when serious antibiotic-resistant infections are on the rise, is a very serious unmet medical need. … New antibacterial drugs are needed to provide treatment options in cases where resistance has eroded the effectiveness of existing drugs."

Woodcock went on to observe the unique economic challenges impeding the development of new antibiotics: "Antibiotics are generally viewed as less profitable by companies and venture capitalists because of their relatively low price and because they are generally taken for a short period of time and often for only one course of treatment by any given patient. Compare this to the long, dependable income stream from a diabetes medicine or blood pressure medicine that patients often take for the rest of their lives or the relatively high price associated with cancer and some antiviral drugs."

Despite this recognition of the market challenges, the administration appears to be focused solely on improved stewardship. On June 13, the Centers for Medicare and Medicaid Services (CMS) released a rather punitive proposal that would require hospitals to adopt strategies to curb overuse of antibiotics or risk expulsion from Medicare. Medicare already penalizes hospitals for patients who acquire infections during a hospital stay. But CMS argued the infection control rules had not been updated in 30 years, and the crisis requires more vigilant monitoring. The CDC found that only 40 percent of hospitals had an antibiotic oversight program in 2014.

This is all well and good, but how do policies focused on hospital compliance encourage development of new antimicrobials when the superbugs eventually overwhelm the current regimen? The administration offers no proposal in this area.

In September 2014, the President's Council of Advisors on Science and Technology (PCAST) — a broad group of experts from academia, the hospital front lines, and industry — responded to President Obama's request for "actionable" items to counter AMR (antimicrobial resistance), issuing an initial set

of economic incentives, and finding generally: "PCAST believes that there is no way to sustain a robust pipeline of antibiotic development without a major influx of private investment. This will require substantially changing the economics of drug development."

But *none* of PCAST's recommendations made it into the President's March 2015 Action Plan for Combating Antibiotic-Resistant Bacteria! What is the point of soliciting counsel from experts if their recommendations are summarily ignored?

CONGRESSIONAL ACTION

Congress attempted to spur antibiotic innovation when it enacted the "GAIN Act" in 2012, with its minor incentives of priority review. Five new antibiotics have been approved since that time—only Avycaz (ceftazidime/avibactam) is considered of high value for unmet-medical-need gram-negative bacteria.

Policymakers still have not touched the fundamental market failure of antibiotics: very low price due to strong downward pressure from the array of generic antibiotics and reimbursement via low-paying inpatient payment schemes combined with deliberately limited volume of sales.

The politics and price of changing the economics of this market are not easy. PCAST found that annual investment of $800 million is necessary to average one new licensed antibiotic per year. The UK *Review On AMR* similarly recommended a global system of market entry awards in the amount of $800 million-$1.3 billion to develop unmet-need agents. So, to create an ongoing pipeline of these products will cost tens of billions. Some members of Congress are developing creative ideas to address these challenges.

IMPROVED REIMBURSEMENT IN MEDICARE

Antibiotics are typically utilized by hospitals in an inpatient setting where reimbursement is controlled by predetermined payment bundles that do not account for the cost of innovative medicines. This incentivizes hospitals to utilize the cheapest drug, deterring use of loss-leading novel therapies. Medicare's New Technology Add-On Payment (NTAP) program is supposed to provide additional reimbursement for innovative products that do not fit well under this capitated payment scheme, but only one antibiotic has qualified since the program's inception in 2001. Moreover, NTAP covers only part of the acquisition cost of a qualifying drug and then for a temporary basis of two to three years.

Recognizing these deficiencies, Congressmen Roskam (R-IL) and Danny Davis (D-IL) introduced legislation that would fundamentally reform NTAP for antibiotics by paying hospitals the average sales price of those qualifying antibiotics that treat unmet medical needs, thereby eliminating cost from the clinical decision of the physician and hospital pharmacists. That bill passed the House of Representatives as part of the comprehensive CURES package but has not been taken up by the Senate yet.

TRANSFERABLE EXCLUSIVITY

Members on the Energy and Commerce Committee have considered enhancing the value of otherwise value-less antibiotics not by improving their reimbursement, volume, or IP protection, but by allowing the sponsor company to convey a period (say 12 months) of its own exclusivity to another drug product. The conveyance could be kept by the antibiotic innovator company or sold to another company entirely with unrelated but profitable products. This creative private-sector solution would inherently allow blockbusters for chronic diseases to fund antibiotic development where the economics are unlikely to ever be compelling otherwise.

Such a transfer policy has been supported anew by the UK *Review On AMR* and was supported by the otherwise ignored PCAST. The policy could be limited to products satisfying an unmet medical need and targeting high-risk pathogens.

CONCLUSION

No greater public health threat exists than the inability to treat infectious diseases—antibiotics are the backbone of modern medicine. The development of resistance is a process that cannot be stopped. Resistance arises through genetic evolution, and these new mutations can even be shared amongst bacteria. Without a constant stream of new products to maintain an advantage over these ever-changing pathogens, the future looks bleak. This requires a multiprong effort of improved stewardship and substantial investment in new innovation in pharmaceutical development through a variety of market incentives.

A recent article in *The Economist* stated, "Combining policies to accomplish many things at once demands political leadership, but recent global campaigns against HIV/AIDS and malaria show that it is possible. Enough time has been wasted issuing warnings about antibiotic resistance. The moment has come to do something about it." Bingo! L

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

Barrett Thornhill contributed to this article.

Tunitas Therapeutics

Tackling novel treatment and prevention of the most serious allergies with new science and seasoned business talent.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Tunitas has two arms of products in development for severe allergies, one for treatment, the other for prevention of severe allergies. Epsi-gam is a "genetically engineered bifunctional human fusion protein" containing domains of the IgE and IgG1 proteins that have unique functions on the cells causing allergic reactions. Now in a Phase 1 safety, tolerability, and dose-escalation trial, the drug blocks mast cell activation and production of IgE to halt the reaction. The prevention line is at a much earlier stage, in preparation for clinical trials of vaccines, first for cat, then peanut allergies, and ultimately many others.

WHAT'S AT STAKE

The most interesting aspects of Tunitas are its bold and possibly breakthrough approach to fighting allergies and its atypical marriage of the academic and business, small biopharma, and Big Pharma mindsets. The company's founding scientist, Dr. Andrew Saxon, had spent most of his career doing basic research into allergic pathways and mechanisms. Saxon and his colleagues constructed a protein (GE2) that fused two key molecules in the inhibitory mechanism and showed how it could block mast cell activation, the key trigger of allergic reactions. All of the technology under development at Tunitas came out of that research.

"Andy had never started a company before, but as a preeminent clinician and scientist and someone who saw patients with allergy and asthma every day in his clinical practice, he certainly had a sense that what he was doing in his laboratory could have important therapeutic applications," says Tunitas CEO Nolan Sigal. One day, a casual call from Saxon to Sigal seeking advice led to a business discussion and thereafter to the business itself. "He sent me his papers, and I thought the science was spectacular; after considering the matter together for the next six to nine months, Andy and I decided to start the company."

Sigal had once imagined himself as an academician for life, with "tweed coat and patches on my elbows." But a growing interest in industry led him to a job at Merck in 1983, where he rose up through the ranks of research management for the next 10 years, finally to head the company's immunology program. He then headed drug discovery and development at several biopharma startups before cofounding Tunitas with Saxon in 2007. Now, a large portion of the company's management and science team has immigrated from Big Pharma to entrepreneurial biopharma.

The two arms of the Tunitas pipeline, allergy treatment with epsi-gam and prevention with vaccines, will require maximum dexterity in the company's management. Asthma and other serious allergies are huge and fast-growing markets; asthma alone has about 25 million U.S. sufferers. But epsi-gam will be a specialty, rather than primary-care, drug, treating the relatively small, but still impressive population of 2 to 3 million patients whom existing agents fail to help. Tunitas is smart to have established a manufacturing base early in development — it will be critical to clinical development — but the company may also need a commercial partner on board following Phase 2 trials to address actual asthma practice and market conditions.

"We have taken all the possible steps in early development to achieve a great deal of confidence," Sigal says. "If what we have seen in cell culture and in nonhuman primate models translates to actually working in people, we know we have a great drug." Following the Phase 1 results, Tunitas plans to file an IND (investigational new drug) application for epsi-gam in the United States by the end of 2016, then begin Phase 2 studies early the following year to test the drug's effect on allergy symptoms. From this small company, and the academic lab before it, a mighty business may grow.

NOLAN SIGAL CEO

Vital Statistics

18
Employees

Headquarters
San Francisco

Finances

2010-2014
$9.5M
Nondilutive
(NIH/other grants)

2015
$10M
Series A (Ally Bridge Ventures, WuXi Ventures, RA Capital)

Partner
Patheon
(cGMP manufacture)

Latest Updates

May 2016: Presented on potential of epsi-gam as treatment for allergic asthma at the American Thoracic Society meeting

May 2016: Initiated Phase 1 trial for epsi-gam in Australia; top-line results expected early Q3 2016

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Biopharma Companies Are Focused On Access, Continued Innovation

RON COHEN, M.D. President and CEO, Acorda Therapeutics, Inc.

Our nation is engaged in an increasingly intense debate about our healthcare system, with particular focus on access and cost. Often, the price of medicines is at the center of this discourse.

While some of our industry practices can justifiably be criticized (as they may be for any industry), I have found the vast majority of the thousands of people I have met over my 30 years in the industry to be passionate, committed people who come to work every day to make a positive difference in the world. And they do!

I believe that, rather than vilifying any segment of our healthcare system, we need to have an open and frank dialogue about the costs of this system — one that includes all the players that are needed to help improve care and affordable access: biopharmaceutical companies, hospitals, physicians, payers, regulators, legislators, employers, and patient advocacy groups.

Our shared goal should be to design an economically sustainable system that ensures patient access and promotes future innovation. Here are a few keys to consider as we work toward this goal:

- We need to explore new ways to develop and deliver medicines that maximize patient benefit and drive smarter spending within the healthcare system. Such approaches include value- and outcomes-based contracting arrangements that reflect the different values medicines can have for different subpopulations. We must also emphasize patient adherence and education programs, alternative financing and payment mechanisms, and other options.

- Legislators must remove legal barriers that currently limit or prevent the pursuit of innovative approaches. Such barriers include antiquated pricing requirements for government payers, which interfere with the ability to implement new value-based pricing models. Companies are also restricted in the information they may share about their products. Removing restrictions on truthful, nonmisleading communications about medicines can enable more effective discussions between drug developers and payers, improve healthcare outcomes, and save money.

- Any discussion on drug pricing needs to account for the "innovation ecosystem" that produces advanced new medicines. The reality is that the great majority of drugs in development, almost 90 percent, fail; and over 90 percent of the over 1,000 biopharma companies are not profitable. Yet the failures must also be invested in, to allow the successes to emerge. Investors must be confident that they will have large returns for the few winners in order to justify their continued investment in drug innovation — otherwise they will default to less risky investments, and we will not have the medical breakthroughs we need.

- It's also important to understand that these high returns last for only a limited period of exclusivity. After that, the drugs become generic and are available cheaply forever after. This is a great bargain for society. No other segment of the healthcare system reduces prices after a fixed period: hospitals don't lower their rates after they have paid off their mortgages; nor does the price of your health insurance premiums drop by 90 percent after 10 years. To put this in context, generic versions of branded medicines are estimated to have saved about $1.5 trillion in medication costs over the past 10 years alone!

- Often lost in the rhetoric is how drug costs fit into the bigger picture of overall healthcare spending. Drugs comprise less than 15 percent of overall healthcare spending, yet are a key part of the system that actually can reduce overall healthcare costs. As just one example, the recently introduced cures for hepatitis C cost about $50,000 per person net

“We now face the real risk that short-sighted policies will drive investors away and impair the U.S. biotech sector that drives global medical innovation and employs more than 800,000 people across the country.”

of rebates, yet have been estimated to save over $200,000 in healthcare costs associated with the complications of hepatitis C. Effective prescription drugs help hold down overall spending in ways that are not always immediately apparent. The patient who does not have to go back to the hospital after a successful course of treatment rarely makes headlines.

- A related point on drug prices is that, like the “rack rate” in hotel rooms, virtually nobody actually pays the list price. Payers and their agents negotiate vigorously with drug manufacturers, and numerous other parties, such as distributors, hospitals, and pharmacies, and also take a percentage off every dollar of the nominal drug price. Thus, the total discount to the list price may be up to 50 percent or more. And, while prices for some drugs have indeed increased substantially, overall branded net drug prices increased just 2.8 percent in 2015, less than the increase in insurance premiums.

- But still, aren’t the Big Pharma companies reaping “excessive” profits? The top 10 biopharma companies have an average return on equity of about 20 percent. That’s good, because it is sufficient to continue to attract investors. But this rate of return ranked only 42 behind such industries as information technology, restaurants, home improvement chains, apparel, footwear, and beverage companies.

- The biopharma industry invests more in R&D, as a percentage of its revenue, than any other industry. You might not know it from reading today’s headlines, but biopharma companies invested more than $70 billion in R&D in 2015 alone, almost triple what the NIH spent on R&D.

- It’s time that outliers like Turing and Valeant stop being held up as representative of the biopharma industry; they are not. These companies invested virtually nothing in R&D, while taking huge price increases on old medicines, and they have been rightly repudiated by the major biopharma industry organizations.

- Talking about drug pricing also means tackling the inequities in insurance coverage that force patients to pay a far larger share of their medicine costs than for hospital or physician services. Often this effectively denies them the care they are supposed to be insured for. Why are copays for hospitalizations only about 4 percent, when patients may be forced by their insurance companies to pay 30, 40, or even 50 percent of the costs of their medicines? Insurance companies like to claim that drug prices are causing their premiums to go up. But their own data shows that the major drivers are inpatient and outpatient hospital price increases (accounting for 53.4 percent of premium growth) and professional services like doctor visits (accounting for 21.5 percent of premium growth), not prescription drugs (17.5 percent of premium growth).

In summary, innovative medicines increase our overall health and lower other healthcare costs. They do so at prices that are temporary, that lead to low-priced generics permanently, that permit the highest rate of R&D investment of any industry, and also attract the huge amounts of outside investment that are needed to produce the next generations of innovative medicines. We now face the real risk that short-sighted policies will drive investors away and impair the U.S. biotech sector that drives global medical innovation and employs more than 800,000 people across the country.

Does this mean there are no problems with drug access and costs? No. What it means is that the biopharmaceutical industry is one of several important players in the healthcare system, and effective solutions require all stakeholders in this system — drug innovators, payers, and hospitals, as well as regulators, legislators, healthcare professionals, and patient groups — to collaborate to ensure that patients gain affordable access to the medicines they need, while allowing innovator companies to continue investing in the groundbreaking cures and treatments of tomorrow.

BIO’s Principles on the Value of Biopharmaceuticals commit our industry’s leaders to find patient-centered solutions to the challenges and opportunities presented by modern medicine. To date, we are the only sector of the healthcare system to produce a document of this kind. A productive discussion should be less about finger-pointing, and more about collaborating to improve outcomes and maximize the effectiveness of healthcare dollars.

We stand ready to work with all parties to that end, and will continue our efforts to improve healthcare outcomes, and access to those outcomes, for all people who need them — now and in the future. L

RON COHEN, M.D., is president and CEO of Acorda Therapeutics, Inc. which he founded in 1995. Dr. Cohen is chairman of the Biotechnology Innovation Organization (BIO), and serves on the Board of Directors of VBL Therapeutics. He previously served as Director and Chairman of the New York Biotechnology Association (NYBA).

PHARMA, PAYERS, & PATIENTS

Finding The Common Ground On Drug Pricing

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

From conversations spring beginnings. People share ideas and typically go away with some new ways of acting on them. But reaching resolutions presents a greater challenge than simply sparking initiatives, especially when the voices in a conversation speak disparate views. Of course, a group whose members all share an obvious common interest will have an easier time of it, though their discourse may lack much drama or their resolutions much impact for anyone outside their circle. If you want to resolve a real conflict — to reach a solution that works for all stakeholders — you must start a conversation that includes, at least, a fair sample of the opposing sides.

So when we decided to implement an advisor's proposal to hold a roundtable on drug pricing, we also chose to apply the principle of inclusion. We not only invited roundtable candidates from the biopharma industry, but we also reached out to some of the industry's most powerful adversaries: healthcare insurers, or "payers," managed care organizations, and pharmacy benefits managers (PBMs). And we recruited other panelists from organizations that fight for patients' access to medicines — some of the strongest supporters of industry innovation, but now also an emerging voice of conscience for industry pricing practices. Two additional panelists, a Harvard economist and a veteran industry strategist, helped widen the context when the discussion turned to "value pricing" of innovative new drugs.

The panel included three essential perspectives: the payers' and other outside advocates' side of the debate; the industry/business case for drug pricing; and the need for solutions based on acceptable terms for all parties. Although panelists stopped short of writing precise prescriptions, they found value in sharing views and envisioning new directions for potential solutions all stakeholders may achieve together, given enough time, work, and goodwill.

THROUGH AN OPEN DOOR

We are hereby including our large body of readers in this conversation as well. We hope to break out of an old pattern — the industry discussing pricing issues almost exclusively with itself, mainly behind closed doors. In the following edited transcript of the roundtable exchange, we take you into the room where our panelists gather around the table and speak directly to each other's concerns.

Chief Editor Rob Wright greets the panel and shares his perspective on the roundtable's central focus — perception versus reality in the drug pricing debate.

HOST: ROB WRIGHT
Chief Editor, Life Science Leader

Welcome everyone to this morning's very important discussion of drug pricing. We are in Boston, where my daughter will be attending Berklee College of Music in the fall, leading me to compare rising healthcare costs to rising higher education costs. Since 1978, the cost of getting a four-year degree has increased by 1,120 percent, four times the consumer price index, while medical expenses have increased by 601 percent.

We all know the value of a four-year degree, but it's costing a lot more, taking a lot longer. Sixty percent of students now take six, not four, years to earn their degree. But on the healthcare side, we have seen HIV and AIDS being changed from a death sentence to management of a chronic disease. Today, if you're diagnosed with cancer, there is a 50 percent chance you will survive at least 10 years. Now we have a hepatitis C drug that is priced much less than the previous lifetime therapy and eliminates the need for a half-million dollar liver transplant.

Nobody is calling the universities and the colleges greedy profiteers, but there is a lot of finger-pointing at the drug industry. We're hoping to move toward a more balanced view of the industry today, and at the same time, toward ways industry can work in greater harmony with payers, patients, and the public in general.

MODERATOR:
WAYNE KOBERSTEIN
Executive Editor, Life Science Leader

This is not a new debate or a new issue in the pharma industry, of course. But the players have changed, and the balance of power has changed. At this table we have voices for the key players ready to speak. This could be the beginning of a new conversation for all of you. Each of you can say where you see the problems and where you see some possible solutions, but we also encourage you to listen carefully to each other as the discussion proceeds. It can be said patients inhabit the common ground we seek, so we will start with the patient's perspective.

ELIZABETH PAGE
Co-Chair, National MS Society Advisory Committee on Access to MS Medications

This is something people with MS have been dealing with for a long time. There have been decades of increasing prices, and it has changed the landscape for our population. I'm not the only patient here today. We all access healthcare, and anything that happens in this industry that impacts cost and access to care and medications affects all of us. Normal market forces are not at play when you talk about this issue — particularly in the world of MS, where we have increasing competition in the market, yet the prices are rising at a staggering rate. As each new agent enters the market, it is priced higher than the existing ones, and existing agents follow suit.

What value do I put on my medication? I am on one of the first-generation MS medications and have not had an exacerbation in more than 10 years. All medications don't work the same for everyone, and in some of us they overachieve. But the medication was dropped from one of the largest PBMs this year, though not the one that supplies me. Cost is driving new utilization management measures on the payer side.

In an MS Society survey of more than 8,500 people with MS, we were surprised to learn 40 percent of the respondents are receiving patient assistance from pharmaceutical companies. Yet 40 percent reported it was difficult for them to afford the medications, and 79 percent believed the prices were unreasonable. A disproportionate burden of the cost is born by certain groups. A single medication in a class may support the development of the others within that class. MS drugs may be priced at a place where they support the development of, say, Alzheimer's medications.

If decisions are patient-centered and patients can access, change medications, and stay on therapies best suited for them, they will be healthier, and cost in the system will be lower. Anytime we reduce the pressure of cost, it will lead to a more sustainable, transparent system with more predictable outcomes.

MARGARET ANDERSON
Executive Director, FasterCures

In the patient advocacy, not-for-profit philanthropy community, many of the pioneering organizations partner with industry and de-risk the science to get industry to develop it. We care deeply about innovation. So the drug-pricing issue, and the fervor of the headlines it has generated, have taken some of our groups by surprise. Patient-advocacy groups were created mainly because there were no effective therapies in their particular disease areas. We have been somewhat disinterested in fixing the healthcare delivery system because it didn't relate to that core mission of de-risking the science, but now we are learning about it. If we can start to look at the healthcare delivery system, the healthcare costs, and the role innovative therapies can play in reducing long-term costs, it could be an effective wedge, but it will not happen overnight. We have asked payers to join us in discussions, but they have shown little interest to date.

HEARING THE OTHER SIDE

Our "payer" panelist offers an alternative context for the drug-pricing debate.

TROYEN BRENNAN, M.D.
Executive Vice President,
Chief Medical Officer, CVS Health

The opening introduction really should have compared the average wage of the average worker in the United States, which is flat over time, to the rising cost of healthcare, including pharmaceutical cost. Real wages just have not increased much at all over the course of the last 10 to 15 years. Moreover, as the baby boomers age, we have fewer and fewer workers per retiree — therefore we cannot hope to afford the system we currently have. That is where the real crisis comes from. Anyone who takes an ethical view of managing healthcare is basically saying there's a commons issue here, and if you all overgraze the commons — consuming shared resources to the point of harming the system on which everyone depends — it will eventually lead to disaster. That is the payers' point of view.

We negotiate with pharmaceutical manufacturers, and we develop formularies. Our basic business model is to offer the lowest cost possible for the right medications to our clients: managed care organizations, health plans, and employers. To manage drug costs, we take advantage of competition between drug companies for essentially identical medications in the same class to get the best possible price; and we ensure through prior authorization that prescribers are following evidence-based medicine.

Our PBM also has a possibly novel bulwark against reducing access to needed care: an independent pharmacy and therapeutics committee, consisting of about 25 doctors and pharmacists. They independently review and decide about formulary placement and utilization management. We have several hundred other expert doctors and specialty panels to review all of our programs. So, for example, if we want to remove a neurology drug from the formulary, it has to go through

a neurology expert panel and then through our P&T (pharmacy and therapeutics) committee, who must be convinced good alternative medications are available in such situations. They also must approve any of our requirements for prior authorization of specific drugs.

ROBERT EASTON
Co-Chairman, Bionest Partners

Everybody seems to think the price of drugs has gone up, but it has actually gone down over the years, quite dramatically. Today, 90 percent of the scripts written in the United States are generic, and essentially every one of those scripts is at a lower price than it was each year before. The price of specialty and rare-disease drugs, however, is where the whole discussion should focus because it is the only place where price inflation has occurred. In the mass markets like hypertension, which 20 years ago was the biggest problem we had in this country, the price of drugs has gone down by half — because of a wonderful price-control system called mandatory substitution.

PATIENTS IN THE MIDDLE

The panel turns toward more specific cases where companies, patients, and payers spar over prices.

JEREMY LEVIN, D.PHIL.
Chairman and Chief Executive Officer, Ovid Therapeutics

The issue is less about pricing than the fact that no patient ever wants to take a drug. Having to take a medicine represents a very significant step in the patient's life. But buying and paying for a drug is not the same as purchasing a free-market product. Patients generally don't even know the price of their medicine. Although medicines are part of one of the key pillars of our democracy — education, defense, and healthcare — medicines do not operate in a free-market environment. Patients are therefore not traditional "customers." Our responsibility as an industry is to understand the implications of this fact.

We need to be the patients' advocate and ally, and they need to be our advocates. Because until they are, policymakers, whom the patients elect, will continue to paint a big bull's-eye on us. It is a mistake for us to be debating the drug-cost issue with pharmacies, payers, versus tackling the issue together. The mutual task for pharma and all these stakeholders should be attaining better, cost-effective patient care.

GEORGE SCANGOS, PH.D.
Chief Executive Officer, Biogen; Chairman, Pharmaceutical Research and Manufacturers of America (PhRMA)

Drug prices as a percentage of healthcare cost haven't changed over the past 40 years, and the percentage is unlikely to change. But the point is patients show up at a pharmacy counter and they're hit with co-pays, co-insurance, or full payments against deductibles they can't afford. We should not be in a situation where patients can't afford to fill their prescriptions or have to make other sacrifices to do so.

We have to be part of the solution, but we can't solve the problem by ourselves. We must work together to figure out how to evolve the system so patients can actually afford the drugs they need, but in a way that doesn't dis-incentivize the development of new drugs. I'm the CEO of a public company; I have responsibilities to the company's stakeholders, and the biggest stakeholders are the patients who take our drugs. When we price our drugs, we must consider the value of how they affect the patient's health, lifestyle, quality of life, family, and so on. We must also consider systemic affordability.

Troyen is correct — healthcare costs are rising faster than is sustainable. We all have to participate in finding solutions to that issue. Ensuring the proper use of the right drugs by the right patient should be cost effective. Some pay-for-performance schemes could be good, although regulatory constraints make them hard to negotiate. Payers must also consider some changes — they have put a great burden on patients by increasing "cost sharing."

MISSION POSSIBLE?

Has a payer-sponsored PR campaign poisoned the waters for constructive drug-pricing discussions?

RON COHEN, M.D.
President & CEO, Acorda Therapeutics, Inc.; Chairman, Biotechnology Innovation Organization (BIO)

I hear many learned and thoughtful comments around the table. But as I listen, I realize how almost impenetrably complicated this issue is. The current environment is utterly not conducive to even beginning to find practical solutions because it has become so charged. A few years ago, the AHIP [America's Health Insurance Plans] association decided to fund a campaign that would focus attention on the drug industry and drug pricing. They have been very successful.

The AHIP asked Hep C patients on Sovaldi, "What do you hate about our system?" They said, "My drugs

are too expensive." They were not talking about Sovaldi's list price of $84,000 or probably $50,000 with 45-percent discounts — in exchange for which society probably gets about $200,000 back in avoiding lifetime care — they were talking about what they would have to pay out of pocket due to insurer policies.

It is not possible to have constructive solution-seeking conversations right now when one of the key players, biopharma, is being publicly and intentionally vilified by other parties. What hasn't been thrown into the public spotlight is how hospitals and the insurance industry contribute to all of these issues in at least equal measure.

According to IMS, drug prices for patent-protected brand drugs in the U.S. grew only 2.8 percent from 2014 to 2015 — after rebates, discounts, and other price concessions were taken into account. Overall sales of pharmaceuticals was $425 billion, but overall revenue for pharmaceutical companies was $310 billion. What happened to the $115 billion of drug sales? It went to the PBMs, insurers, hospitals, and all the other players who take a piece of the drug spend along the way.

KOBERSTEIN: Are the patient groups seeing more concern about cost sharing and the other measures by payers that restrict access to drugs?

PAGE: Absolutely. Many of the decisions with step therapy for MS are being based on the cost of the medications, not medical benefit. All of the MS medications end up on the top tier. Patients have no financial choices among drugs. With prior authorization, patients frequently must get reauthorized repeatedly. The shift from co-pay to increasing levels of co-insurance makes drugs unaffordable for many patients.

Troyen, I would encourage you to bring some patients onto your formulary design panels. Let the patients talk to you about the difference among delivery methods. Taking an oral versus an injectable form of a medication might enable some to stay on the medication and get a better outcome in the long run.

ANDERSON: There's incredible work being done to bring the patient perspective and experience into the design process so that we get better products that actually meet their needs. We need to do the same thing on the healthcare delivery side. We are working with Avalere, a strategic advisory company, to pioneer a value framework from the patient perspective. A number of other not-for-profits are also in this space, and we're all talking to each other actively. People working on the value frameworks seem shocked at how much fervor the frameworks have generated. When we asked them, "Where's the patient perspective in your framework?" they say, "That wasn't what we were starting out to do." That is another great opportunity for the patient voice and the patient movement to play a role in the value dynamic, but we will need industry engagement to broaden the focus of these frameworks.

PAYING FOR INNOVATION

The panel gets down to tackling the economic relationship between drug pricing, access, and development.

KOBERSTEIN: Arm in arm with the issue of healthcare cost is the issue of patient access to healthcare. It isn't just about making choices based on value. In our system, to receive any assistance for the noninsured financial burden of care for patients with catastrophic conditions, people usually have to exhaust most of their resources first. Let's turn to our economist.

AMITABH CHANDRA, PH.D.
Malcolm Wiener Professor of Social Policy; Director of Health Policy Research, Harvard Kennedy School of Government

It is true, when U.S. patients get sick, they face double jeopardy. They are already hit with the disease — cancer, MS, Alzheimer's — and then they get hit with the co-insurance and copayments. That's not insurance anymore because the purpose of insurance is to smooth out well-being; it's not to make sick people shop for healthcare. That should have been done while they were healthy. And so we need more innovation in plan offerings, especially with a value-based plan design where we don't have co-insurance for things that work.

Second, on the point of development, it is entirely possible that we, as a society, might be innovating at a rate that the average American can't actually afford. We have built a system where we have never actually sent a signal to manufacturers saying this is how much we can afford as a country. Instead, we dodged the issue of willingness-to-pay with laws that force Medicare and Medicaid to cover every FDA-approved drug. That's essentially saying, "If you build it, we will pay for it." Then manufacturers build it, and we say, "Well, now we don't want to pay for it." This kind of pricing uncertainty will affect development, which is already risky.

Third, academics love to say there is no trade-off between innovation and pricing. This comes from our self-interested belief that scientific progress, often in our labs, generates innovation, instead of also realizing that market size induces innovation. So the fewer people we insure or the less we pay, the less innovation we will get. The trade-off is exacerbated where biopharma competes in financial markets for investor dollars with Apple, Uber, and other high-tech companies. The higher the financial returns to tech, which is not as R&D intensive as biopharma, the fewer the dollars that will flow to biopharma. So what happens outside healthcare, in the rest of the economy, affects R&D in biopharma, too.

WILL INVESTORS FLEE?

Major investors, nervous about the drug-pricing controversy, are contemplating wholesale flight from the biopharma sector.

COHEN: A couple of months ago, George and I were sitting around the table with the portfolio managers for some of the world's biggest public mutual and investment funds — altogether representing more than $500 billion worth of capital. They are extraordinarily exercised about what they are seeing in the entire price-value debate. They conveyed this message very clearly: They will no longer be able to allocate the current level of capital to medical innovation if the debate continues along the same path. If we simply reduce pricing in a vacuum, with no other action to incentivize investment in our industry, we will significantly reduce the level of innovation and the number of important new drugs.

SCANGOS: If you cut industry profits in half, you save only a tiny fraction of total healthcare costs at the expense of a huge reduction in the flow of new drugs. I don't think anybody wants to make that trade-off. We do have the problem that patients can't afford their drugs, but the solution is not to slash the industry's profits. There has to be more thoughtful ways of cutting costs that would yield much larger results.

CHANDRA: The tremendous opportunity is the realization that most of healthcare is a noncompetitive industry. The hospitals are huge geographic monopolies. My greatest worry is that biopharma will also become consolidated because of the pricing uncertainty that smaller biopharma companies face. In that world, biopharma prices would be high for two reasons— because the R&D is expensive and uncertain, and because of reduced competition. The more competition we have in biopharma, the better it is for patients.

One theory for reduced price competition in biopharma may lie in the U.S. Patent Office. The standard to get a patent in the United States is extraordinarily high. It is very hard to show that a molecule is novel and nonobvious when that molecule has been talked about at the major science meetings and published in leading scientific journals. If we could lower the patent bar, we would see more new drugs, and more price competition.

RETHINKING THE SYSTEM

The roundtable steers back toward to its original mission — seeking practical solutions all sides can accept.

COHEN: Biopharma is looking at long-term innovation, with reduction of healthcare costs because of better treatments. Payers are looking at this year, this quarter, how do they cut costs now. Under their accounting systems, I'm not sure they can amortize cost savings from a particular medication over time.

CHANDRA: We treat the payers like regulated utilities and that reduces innovation by payers. We, as in our government, made the payers regulated utilities through Medicare's MLR [medical loss ratio] rules and similar measures. And so we can't enter into a long-term contract with a payer, which is why the payers don't do prevention.

DAVID MEEKER, M.D.
Executive Vice President,
Head of Sanofi Genzyme

We all agree some drugs are priced too high, but we would have a difficult time agreeing on which drugs in particular. As an industry, we've fallen into the trap of trying to defend everyone's price. That is not our job. Each company's job is to defend its own prices.

What really drove innovation in the rare-disease space was the business model our company created. We priced our first orphan product, a true rare-disease drug for only 5,000 people, at $400,000 a year. We ended up in the headlines and even in front of Congress. But we built a new business model, and through that model, there are now hundreds of orphan drugs available that would have had no chance without it. But orphan designation does not mean orphan pricing. An orphan drug for 200,000 people and an orphan drug for 5,000 people represent very different price points. All of us have responsibility in this equation, yet we're not good at listening, and we're remarkably short of facts and reliable data to inform the debate.

LEVIN: The range and dialogue on pricing from the very small orphan or rare area to the very large markets are substantial. But the debate in the orphan area has not begun substantively. We all would agree that fixing this system is critical because the system itself is too important to fail. Without doing so, as a society, we would change dramatically through our inaction. Without doubt, the industry is getting punched every day of the week. However, I believe part of the solution is to look at the system and to ask ourselves where we can become partners with other stakeholders in finding remedies for the system's ills instead of arguing about the fairness or otherwise of pricing.

COHEN: Pharmaceuticals-biopharmaceuticals are the only component of healthcare that can reduce costs for society. People are still struggling to figure out what kind of value framework makes sense. We need a framework for talking about the entire healthcare experience for the patient in assessing the relative value of those components.

LEVIN: Your comment might better be that drugs are the only component believed able to reduce costs in the system — this is a sound bite that the Hill understands. But it is not the sound bite that the patient can understand. Nor is it accurate. As an industry, we need to build a deep relationship with patient advocacy groups to give, for example, a sense of what it is like when it costs $85,000 per year to care for a patient in a family with Alzheimer's. Medicines can dramatically reduce that cost.

CHANDRA: The government tried to make the care-delivery system more efficient, but the solution it picked — ACOs [Accountable Care Organizations] — was completely unproven. The proven solution was bundled payments but for a variety of political and aspirational reasons, we didn't pursue that. Helping government and plans to lead on bundled payments is a much better way to disrupt the hospital industry than to push on ACOs, which have only encouraged more hospital consolidation.

COHEN: Every one of the solutions CMS now proposes under its 340(b) hospital discount program is trying to chip away directly at drug prices rather than taking a systemic approach that forces the market to come up with individual solutions, as in bundling.

SCANGOS: Now the question is what can we practically do in the nearer term to change the system and its incentives? I'm worried about whether we have the time before we witness some kind of populist solution.

WHO IS LISTENING?

The one panelist on the payer side, who has listened to most of the discussion until now, shares his thoughts on what he has heard.

BRENNAN: I would encourage pharmaceutical manufacturers to bring more people into your tent to present the other side of the discussion. I am worried when I hear the same arguments over and over. I don't believe you have a broad and contextual grasp of the situation right now. Take bundling. If I am a medical center taking risk in a bundle program that involves a disease with a specialty medication, I will take advantage of 340(b) pricing if it is available. That is where good business sense will lead me. The pricing is so much more attractive, and because 340(b) hospitals have a disproportionately high share of Medicare and Medicaid patients, they will justify using the discount from an ethical, not just a business point of view. They are the last hope in access for many patients.

Where we're really seeing drug-price inflation is on branded medications, both specialty and nonspecialty, with consistent, annual 20-percent price hikes. If pharma companies want to get out of the spotlight, my suggestion is get your inflation rate back down to where hospitals and physicians have been, 3 to 4 percent during the past few years.

MEEKER: There are bills going through Congress now that would mandate that the FDA approve generics within six months if those generics break a monopoly such as the Turing-Valeant situation. We should all be encouraging Congress to pass that law. It is an easy way to deal with abuses of the system.

COHEN: As trade associations, we are specifically barred from any internal discussions that touch on pricing specifically. We are all independent companies, and everyone makes their own decisions. I don't see a way to regulate behavior other than through more extended conversations, societal pressure, and some of the pressures Troyen talked about. I have no problem justifying a high price for a new innovator drug. Annual increases that are way in excess of inflation are indeed more problematic, though even here the issues can be complex.

MEEKER: We should not take annual price increases that are purely related to increasing revenue, as opposed to price increases which reflect the cost of living or true recognition of increased value creation. We must find a way to talk to payers preapproval. Those are actionable items.

A small-biotech CEO, having listened, enters late in the discussion.

LESLIE WILLIAMS
Founder, President and
Chief Executive Officer, ImmusanT

I lead a venture-backed company, the kind that other companies sitting around the table look to for external innovation. It is a very challenging time for raising capital for a Phase 2 asset in the Valley of Death from investors who are nervous not just about the scientific and regulatory risk, but also how you will price your product.

In that light, we are very patient-focused. We bring patients into roundtables to thoroughly understand their needs. We are also innovating on the manufacturing side, so when we're ready to launch, we have a very cost-efficient drug. We put a lot of capital into understanding the market needs, reimbursement, pharmaco-economics, the works. The dialogue with payers proposed here is something we are doing at the ground floor, in early development.

KOBERSTEIN: Like many good roundtable discussions, this one seems to be just getting going as it ends. We have to look at this as a beginning of a discussion to continue long term. Let us not say the roundtable is over, end of discussion. Let's continue our exchange as a working group to keep moving the ball forward, and as we add other participants down the road.

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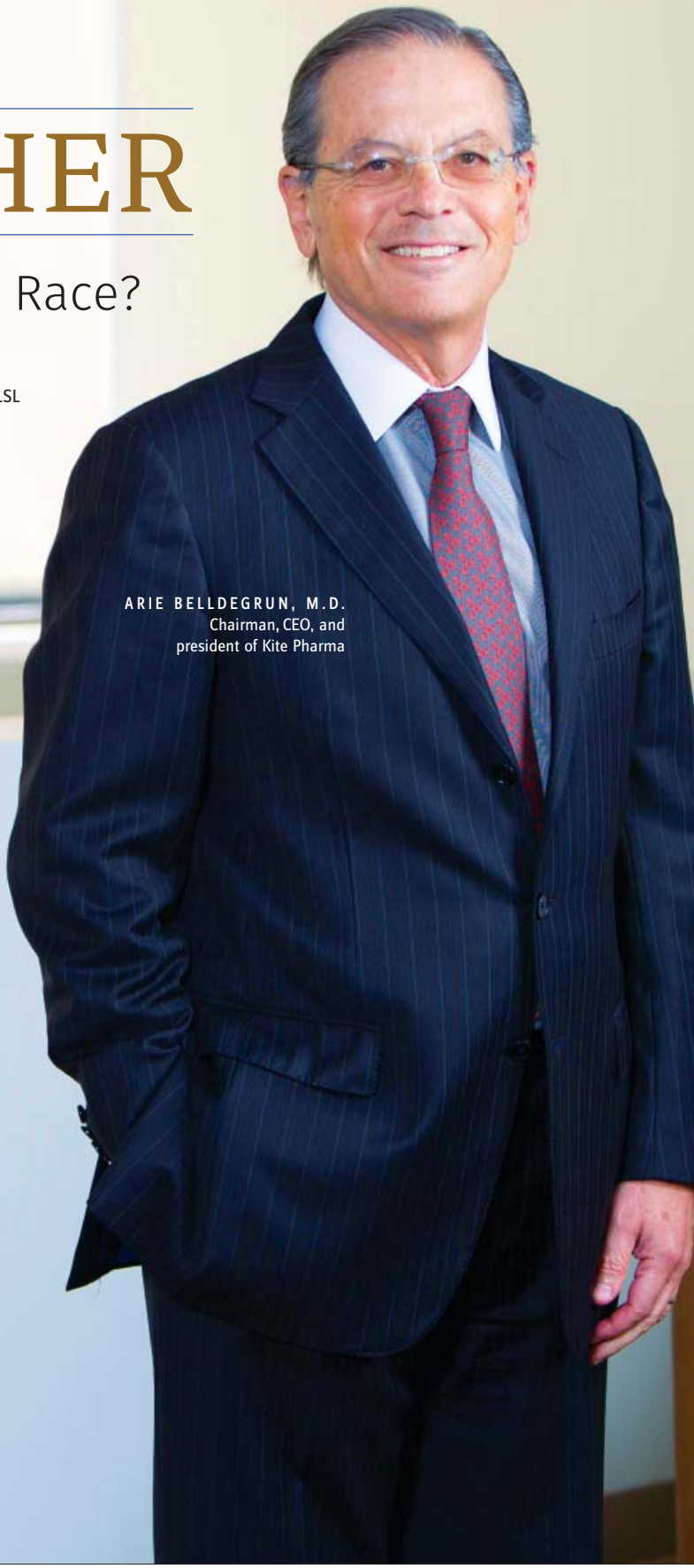
Will Kite Pharma SOAR HIGHER In The Engineered T-Cell Race?

ROB WRIGHT Chief Editor @RFWrightLSL



ARIE BELLDEGRUN, M.D.
Chairman, CEO, and president of Kite Pharma

During Kite Pharma's (NASDAQ: KITE) company presentation at the February 2015 BIO CEO Investor's Conference in New York, Arie Belldegrun, M.D., created a noticeable buzz among attendees when touting the latest developments coming out of the company he founded back in 2009. But having successfully started and sold two biotechs (i.e., Agensys and Cougar Biotechnology), Kite's chairman, CEO, and president knows biopharma investors can be a fickle bunch — often jumping on company bandwagons when early results provide promise of profits, and abandoning ship when returns aren't realized. This is why the biopharmaceutical game, one of lengthy endurance, is best played by those whose attributes include passion, patience, persistence, and probably a good deal of wisdom, too. These are qualities Belldegrun seems to possess in spades.

In the United States, there are currently three companies leading the tumor-targeting engineered T-cell race (Juno Therapeutics, Novartis, and Kite). However, only one can claim to have a physician and current practicing scientist at its helm — Kite.

Belldegrun, who has authored several oncology books and more than 500 scientific medical papers, is also a professor of urologic oncology at UCLA. He sat down with me for this Q&A before oncology's biggest gathering — the American Society of Clinical Oncology (ASCO) annual meeting — to share his insights and why he believes Kite Pharma will soar higher in the ever-enlarging T-cell race.

What Was The Impetus Behind Starting Kite Pharma?

The year we started Kite (2009) was the same year I was involved in the sale of Cougar to J&J. A group of us scientific founders at UCLA were thinking about what would be the next wave of scientific interest to hit the biopharmaceutical community. Through our discussions, we felt it was probably the right time for immunotherapy research to move out from being primarily an academic exercise and into a commercial company. The information and technologies that existed in 2009, in combination with developments that had taken place in cell and gene therapies, such as being able to clone enough genes for a scientist to be able to work with, all seemed to indicate that the time was right to actually build a biotech company dedicated to the development of engineered T-cell therapy. To the best of my knowledge, Kite Pharma was the first company dedicated to what we called, EACT, Engineered Autologous Cell Therapy, which means you take the cells from the patient, you engineer them in-vitro in the laboratory, and you give them back to the patient in a now-superboosted and activated form. I like to think of the engineering process as outfitting a cancer-fighting cell not only with a weapon, but a GPS tracker so it can go directly to the cancer cell to do its job, while sparing normal healthy cells that are nearby.

We had the good fortune to be able to go back to where I started at NCI (NIH's National Cancer Institute) and meet with Steven Rosenberg, M.D. He had continued to develop his immunotherapy research, and I had been keeping up on his work. Rosenberg had several patients he had treated with engineered T cells in two different technologies, chimeric antigen receptors (CARs) and T-cell receptors (TCRs). When we saw the first responses from these few patients, their cancer regression was dramatic, with tumor disappearance only a few weeks following initiation of therapy. In our collective careers, none of us had ever seen this type of response. We clearly understood that this was something quite transformational, and this is why we started Kite Pharma.

As 2009 Was On The Tail End Of The Great Recession, Why Not Wait To Start Kite?

It was in 2008 when we actually started discussing selling Cougar Biotechnology to a major pharma. While it seemed like the right time to sell, it was during the worst financial time in recent memory. But we had an offer which made Cougar one of Wall Street's largest acquisitions of 2009. So while many might have viewed the recession as a time to exercise caution, because everything was so depressed, we saw it as an opportunity. Because most folks were conserving cash, they weren't looking at university IP. As a result, 2009 was a great opportunity for Kite to accumulate a set of IP from different companies and universities. Because of the expensive IP portfolio we were able to collect, we got a tremendous head start on many other companies.

As for financing, the sale of Cougar afforded us the ability to self-finance Kite. Because we didn't have to immediately go out and look for investors, we could focus our effort on the IP component. In addition, because some people had followed me through some prior investments and had done well, angel investors like David Bonderman of TPG Capital, as well as others, were proactively contacting us asking if they could participate in Kite as a startup. As a result, it wasn't until late 2010 that we finally decided to raise a small "A" round of financing. It was much easier to get buy-in from outside investors, since my fellow founders and myself have always been willing to put some of our own skin in the game during every financing round.

What Are Some Of The Regulatory Challenges When A Product Involves A Completely New Field Of Research?

Sometimes, companies are working on therapeutics that seem to fall somewhere between a drug and a product. But the FDA has two arms: CDER (Center for Drug Evaluation and Research), which deals with the drug component; and CBER (Center for Biologics Evaluation and Research), which deals with the biological component. The latter looks at the cell and gene therapy technologies we are developing at Kite. To evaluate the therapeutics we are developing, the CBER branch of the FDA has to have expertise in cells, clinical data, clinical cancer, clinical gene therapy, and the manufacturing process. That's a lot. Now, I am not an expert on the internal workings of the FDA, but when it comes to how they will go about evaluating engineered T cells, it looks like CDER and CBER will have to work collaboratively, since approving such a class of drugs will be an FDA first. Most likely, CBER will be evaluating the cell and manufacturing side, while CDER will be taking a hard look at the data and clinical patient outcomes.

As it stands right now, CBER has primary responsibility for evaluating our product, since they gave us the breakthrough designation. It should be noted that no

biologic that has received a breakthrough designation on behalf of CBER has yet received an FDA approval. Thus far, everything that has been approved for cancer as breakthroughs has gone through CDER. But again, we see this as an opportunity, as the goal of designating a product as a breakthrough is to get the product to the patient more quickly. Right now our timeline for that is very short. We are finalizing our registration studies, which is our last group of studies being prepared for the FDA. If all goes well, we plan to submit the entire package to the FDA by the end of this year, with the hope that it becomes commercial sometime mid-next year. Since the FDA has never approved a class of drugs which are engineered T cells of patients, now reengineered and infused back to the patients, there are a lot of questions of safety and efficacy, which are the prime concerns and responsibilities of the FDA. So, the FDA is going through the process of learning this whole new field as well. While we are all running very fast to help usher in this new era of engineered T-cell therapy, I believe this technology will go well beyond just treating cancer patients, to other diseases as well.

What Are The Differences Among Kite And The Two Previous Companies You Founded?

The first one, Agensys, was founded in 1996. At that time, we were involved in cloning the human genome. We didn't know a whole lot about genes, so the idea for companies like Human Genome Science and Celera was to produce multiple genes or discover new genes, and throw these out to other companies and let them evaluate — basically gene discovery. Agensys was more of a boutique approach. We said let's clone a gene, find a new gene and understand the biology, and then see how we can use that gene to convert it to a drug. From the start of this gene discovery, we began developing a whole battery of monoclonal antibodies. While today, this is now the standard, 20 years ago, developing and humanizing monoclonal antibodies was quite a challenge. Agensys came up with a great list of antibodies.

When I look back at the challenges we had at Cougar Biotechnology, at the time they seemed great, but at the end of the day, we made a pill. We knew this pill had a good chance in prostate cancer and possibly some chance in breast cancer, too. But to stay focused, we developed it just for prostate cancer. Though we all knew the pill was effective, the expertise revolved around taking it through global clinical trials as fast, and as safely, as we could.

These two companies are completely different from what we are doing today at Kite. First, we are working with a completely disruptive technology. Second, engineered T-cell technology will go way beyond cancer. But even in oncology you can develop the T-cell technology for a variety of different cancers. For example, hematologic (blood) cancers (e.g., leukemia, lymphoma) were the first proof-of-concept (POC) that we took to the FDA. This work led to multiyear hematologic collaborations with companies like Amgen, focused primarily on CAR-Ts. However, with CARs we are also working on multiple other products that extend beyond just blood cancers. On the engineered TCR programs, we have multiple collaborations with other companies, such as Bluebird Bio, to develop the next generation TCR cell-therapy products to treat HPV (Human Papillomavirus)-associated cancers. At Kite, we have essentially a platform technology that has the potential to treat every type of cancer. All we need is the right target on the surface of the cells. The new concept today in immunotherapy is that the cell of origin (i.e., where the cancer originates) is less important than what the cell expresses on its surface. So if a cancer cell expresses antigen "X" on the surface, whether it is a brain or kidney tumor, or perhaps a melanoma, it doesn't make a difference, because these are all potential candidates for a treatment that can knock out antigen X. In other diseases, engineered T cells can be developed toward treating nononcology indications such as HIV, autoimmune diseases, and difficult inflammatory bowel diseases. To be successful, depending on the disease, some of these will need to activate the gene within the T cell, while others will have to suppress the gene.

As this is a platform technology, at Kite we decided very early on to develop a manufacturing facility for T cells, yet be agnostic of what will be produced there. This is why we acquired a company called TCF (T-Cell Factory) in Amsterdam. And now we have a commercial manufacturing plant in El Segundo, next to the Los Angeles airport. In addition, we have a clinical manufacturing facility in Santa Monica, where we are now actively developing and producing cells for clinical trials. Each facility is different. What Kite has that is different from the two previous companies I was involved in founding is an opportunity to transform all of medicine, rather than developing just one drug at a time.

How Were You Able To Create A Successful Collaboration With the Government?

One advantage I had was having worked with Dr. Rosenberg as a post-doc fellow. When I went to him expressing the value of his work to the benefit of patients, I also pointed out that despite all this great work, there has never been a drug that has been developed by government organizations like NCI. This is a problem. Dr. Rosenberg was sitting on top of transformational research being used in the clinic. So when I asked him why he had never developed it into a drug, his simple answer was that he didn't know how to do that. The NCI has great mechanisms in place to fund researchers, but doesn't have the mechanisms for how to develop a commercializable product that could benefit so many more people. I told him if he agrees to work with us, Kite could become the commercial arm for the engineered immunotherapy for the specific

project in which he is currently involved. He was very happy to partner with us.

But this is the government, and as such, there are details for how to collaborate with nongovernment organizations. To facilitate collaboration, Kite had to enroll in a cooperative research and development agreement (CRADA), which is essentially a partnership between the NIH and a biopharmaceutical company. This is very different from merely allowing a company to license a government-developed molecule. Because the scope of what we wanted to do was so large and involved doing joint R&D, collaborative clinical trials, and moving technology out from NIH and improving it in our manufacturing plant, it took us two years just to sign the deal. Because so many different agencies and the government had to be involved, the transfer went all the way to the desk of the president of the United States, as well as the heads of the NCI and NIH. It was a long process; and while two years is a long time, and admittedly did involve some frustration, the relationship we have forged with the NCI is second to none. We have weekly conferences and visits. The NIH is sending people to work with Kite, and vice versa. The collaboration is very active. The benefit for us is that we can tap into the best brains at the NCI to work on engineered T cells. Though I had trained as a post-doc at NCI, doing business with a government entity was something completely new to me.

Since the signing of that initial CRADA, we have expanded this relationship to other departments beyond that of Dr. Rosenberg. Some of the people we started working with, who are great scientists who started off as fellows like me, are no longer working with Rosenberg, but continue working as independent investigators at the NIH. So we had to go through the whole CRADA process again to keep these folks involved. Now we have three CRADAs with three different units at the NIH. Of course, we learned to do it quicker. The fact that we had established a great deal of trust expedited the process, while minimizing the bureaucracy that can often come with partnering with large government organizations.

But this isn't a one-sided relationship, as the NIH benefits from us as well. We are paying them an annual fee and supporting the research in their labs. If we sell the company, they will have a significant royalty stream.

Given The Work At Kite Is More Of A Platform And A Process, Is There Any Concern With IP Challenges Similar To What We Saw With Mayo Collaborative Services Versus Prometheus Laboratories?

We have put a lot of effort into securing our technology. Basically, there are three types of IPs that are a focus for Kite. One is the engineering of T cells. Early on, we secured very broad IP patent protection on the creation of CARs. While the notion of engineering a T cell to be able to find and kill a cancer cell seems well understood and straightforward today, such was not the case some years ago. Therefore, IP patent protection was given to five different institutions, all of which license to Kite. So basically, we own the license for the creation of CARs. Another type of IP is the process by which we are creating this factory for T cells. This is the secret sauce, and therefore, everything that we are doing is proprietary to Kite. For other companies, the process is proprietary to them. Some can be patented and some cannot. There is a very complicated way of producing, simplifying, and automating manufacturing, and each company has its own IP on that particular group. The third piece of IP is the antigen on the engineered TCR. That antigen is something you are licensing from scientists. We now have about seven types of genes from which we are developing the therapy. We license these from the NIH, as well as other places. There's a race to have more and more targets for IP.

While the IP map is pretty clear in the U.S., outside of our borders, it becomes much more convoluted. For example, I had a delegation visiting from China the other week. During their visit, I was informed by a leading Chinese health authority that there are 500 companies in China working to produce CARs. Though I was shocked, it gives you a glimpse of the proliferation that is taking place around Kite's technologies. In the United States, it's much more regulated and a completely different system. Both of our competitors (Novartis and Juno Therapeutics) have similar transformational data on patients that failed every possible therapy. However, one point of differentiation is at Kite, we have the longest follow-up data on patients who are alive and well without cancer for over three years. Keep in mind that at the time of their diagnosis, they probably had a life expectancy anywhere from three to six months. We will be sharing this information, as well as insights on what we see as being the future of engineered T-cell therapy, at this year's ASCO meeting in Chicago. L

Why Animal Health Is The Next Big Growth Area

CATHY YARBROUGH Contributing Editor @sciencematter

The animal health industry is on a growth trajectory, powered by the popularity of pet ownership and a global population hungry for meat and dairy products.

The many large and small companies that develop and manufacture drugs and vaccines for pets and livestock animals are expected to generate $33 billion in sales by 2020, after a record $24 billion in 2014, according to the consulting firm Vetnosis. Wall Street and the European and Asian markets are paying attention. The highly respected J.P. Morgan Annual Healthcare Conference has set aside time for presentations by CEOs of animal health companies. Jefferies and Bank of America Merrill Lynch each have begun sponsoring animal health summits to inform their investors about the sector. For investors based outside the U.S., the first European Animal Health Investment Forum was held in February 2016 in London.

At the 2016 J.P. Morgan conference, Juan Ramón Alaix, CEO and director of Zoetis, a spin-off of Pfizer, said the animal health industry is "evolving from being a small part of pharma companies with little interest from investors to an important and distinct part of the healthcare sector." Zoetis' $2.2 billion IPO in 2013 is often credited with focusing the financial community's attention on the factors that make the animal health industry a promising short- and long-term investment opportunity.

One of those factors is global population growth, according to PwC's August 2015 report, *Animal Health Strategy Playbook for an Evolving Industry*. The worldwide population, totaling 7.4 billion as of March 2016, is predicted to soar to 8.5 billion by 2030. Additionally, urbanization and the rise of the middle class in emerging economies will increase the consumption of meat and dairy products.

"To feed the world in 2030, animal protein production will have to increase by 30 percent from its current level," says Fabian Kausche, global head of research

CONSOLIDATION DEALS IN AH, 2011-2015

DATE CLOSED	TARGET	ACQUIRER	DEAL VALUE ($M)
01/2015	Eli Lilly/Elanco: Sentinel	Virbac SA	
01/2015	Novartis: AH division	Elanco (Eli Lilly)	5,400
01/2015	Novartis (India): AH division	Elanco (Eli Lilly)	14
04/2014	Bioniche Animal Health	Vetoquinol	55
12/2013	Glon Sanders: Lab. Sogeval	CEVA Sante	
06/2013	Dosch: AH division	Merial (Sanofi)	
09/2012	Orsco SAS	Vetoquinol	21
05/2012	Eurovet Animal Health	Dechra Pharma	176
10/2011	CentaurVA Animal Health	CEVA Sante	
07/2011	J&J Janssen: AH business	Elanco (Eli Lilly)	
02/2011	Alpharma*	Pfizer (Zoetis)	345*

**Represents value of Alpharma deal, which was part of the acquisition of King Pharma (total deal value: $3.5B). Note: In addition to the above deals, several major transactions influenced the AH competitive landscape, including Merck & Co.'s merger with Schering-Plough (which included AH business Intervet) and subsequent divestiture of its 50 percent stake in Merial to Sanofi; plus, Pfizer's acquisition of Wyeth (which included AH business Fort Dodge).*

Source: Thomas Reuters, company reports and news, PwC analysis

"The average development time for an animal health product is three to seven years, not that much less than for human drugs and vaccines."

FABIAN KAUSCHE
Global head of R&D, Merial

and development at Merial, the animal health division of Sanofi. "Without effective disease prevention and health management strategies, we'll lose a lot of meat and dairy animals due to disease," Kausche added.

The top five animal health industry market leaders and their reported FY2015 revenues are: Zoetis, $4.8 billion; Merck Animal Health, $3.3 billion; Elanco, a division of Eli Lilly, $3.1 billion; Merial, €2.5 billion ($2.8 billion); and Bayer Animal Health, €1,490 million ($1.7 million).

The animal health industry has profited from the rise in pet ownership and increased spending on healthcare for pets. An estimated 65 percent of U.S. households have pets, and that percentage is expected to increase, said Kausche. According to a 2015 Harris Poll, 95 percent of U.S. dog and cat owners consider their pets as members of the family. "Companion animals over the years have moved from the barn to the garage to the living room to the bedroom to the bed," said Steven Roy, president and CEO of VetDC, one of the numerous small companies in the animal health sector. VetDC evaluates experimental human cancer drugs to determine whether they would be safe and effective in the treatment of pets with cancer. VetDC's leading cancer drug, acquired from Gilead Sciences, is under FDA review for the treatment of lymphoma in dogs.

Because pet dogs and cats are now living longer, they are at increased risk for developing cancer and other age-related disorders such as osteoarthritis, cardiovascular disease, diabetes, and renal disease. Thus, age-related disorders provide niche markets for the animal health industry.

THE DIFFERENCES BETWEEN BIG PHARMA AND ANIMAL HEALTH

The rise in pet ownership and the projected increase in the growing global population's demand for meat and dairy products are not the only reasons that investors are paying more attention to the animal health industry. The R&D cost for a new animal health drug is about $50 million to $100 million compared to more than $1 billion for a human drug, Kausche said. In addition, veterinary drugs and vaccines have a long life. Because veterinary medicine is primarily a cash-based business, third-party payors play a minimal role in the animal health industry.

However, unlike the human biopharmaceutical industry, the animal health sector rarely has produced a blockbuster product. Merial's Frontline flea and tick control product is the only pet medication that has generated annual sales of more than $1 billion, making it the first blockbuster drug for pets.

The most critical difference between Big Pharma and animal health companies is "how quickly we in animal health can translate an idea into a product," said Catherine Knupp, EVP and president, research and development at Zoetis. Unlike biopharmaceutical drugs for humans, experimental veterinary medicines can be immediately evaluated in the intended species. Thus, early in the R&D process, animal health company researchers can determine a compound's safety and effectiveness. "In animal health, we also can look at our 'patients' over a longer period of their life cycle," said Knupp. "So we're able to obtain more specific, relevant, and predictable results about a new drug."

Unlike human biopharmaceutical companies, the major animal health companies develop drugs and vaccines not just for one species, but for multiple species — chickens, cattle, pigs, and sheep, as well as horses, cats, and dogs. Because these different species do not share the same physiology and disease susceptibilities, animal health R&D is more complex than biopharmaceutical R&D. "Dogs are not miniature humans, and dogs and cats do not always have the same health conditions," said Knupp, who spent 18 years in R&D on human biopharmaceuticals before joining the Pfizer animal health division that led to Zoetis.

Like the R&D process, the regulatory requirements in animal health and biopharmaceuticals are "comparable in terms of complexity," Kausche said. In the EU, a single regulatory agency, the European Medicine Agency, is responsible for animal health drugs and vaccines. The U.S. regulatory agencies for animal health therapies include the USDA, EPA, and the FDA's Center for Veterinary Medicine. While the USDA reviews applications for new animal vaccines and biologics that act through the immune system, the FDA has purview of small molecules and other animal health drugs. The EPA plays a role in the review of new

compounds against fleas, ticks, and other parasites.

Despite these differences, animal health R&D is basically a smaller-scale model of human biopharmaceutical R&D and is just as demanding and rigorous. "The average development time for an animal health product is three to seven years, not that much less than for human drugs and vaccines," Kausche said. The time frame for animal health drug R&D may become longer as a result of the industry's increased focus on new compounds and technologies, such as complex mAbs (monoclonal antibodies).

Merial and Zoetis have developed first-of-their-kind mAbs animal health therapies. When it was introduced in 2009, Merial's mAbs cancer vaccine for dogs with stage II and stage III oral melanoma was the first USDA-approved therapeutic vaccine for the treatment of cancer in either animals or humans. In 2015, the agency granted a conditional license to Zoetis for its novel mAbs therapeutic to help reduce the clinical signs associated with atopic dermatitis in dogs.

"In animal health, we also can look at our 'patients' over a longer period of their life cycle. So we're able to obtain more specific, relevant, and predictable results about a new drug."

CATHERINE KNUPP
EVP and president, R&D, Zoetis

THE DIFFERENCES BETWEEN ZOETIS AND MERIAL

Zoetis is the only one of the top five animal health industry leaders that is not part of a Big Pharma company. "Because Zoetis is not tied to another company's priorities, we are able to establish our own customer-driven priorities and can collaborate with anyone and everyone," said Knupp. Zoetis collaborates with more than 100 academic labs and other companies because, "we don't have all the answers and capabilities," she said. One of the company's research partners is Oakwood Labs in Ohio. Zoetis and Oakwood scientists are working together to design a sustained-release injectable pharmaceutical for both pets and livestock. By lengthening the time between treatments, extended-release formulations should reduce the number of injections required to treat the animal.

Unlike Zoetis, Merial is a division of a global biopharmaceutical company. The R&D groups of Merial and Sanofi work together, said Kausche. "We have access to each other's pipelines, technologies, and scientists," he said. Merial also has forged more than 50 external research collaborations with small research companies as well as academic labs. "We also collaborate with governments globally. For example, when an epidemic of foot-and-mouth disease erupts in a country, Merial collaborates with the local government to quickly deliver a vaccine against the specific viral strain affecting the local livestock," said Kausche. Foot-and-mouth disease can be economically devastating. The U.K. outbreak in 2001 affected an estimated 10 billion animals and cost the country $15 billion.

The virus responsible for foot-and-mouth-disease cannot infect humans. However, many animal viruses and other microbes can be passed to humans. "Sixty percent of infectious diseases in humans are zoonotic, passed from animals to humans," said Knupp. Merial and Zoetis are among the animal health companies that stand ready to respond quickly to the possible emergence of a new zoonotic infection. "By having research centers around the world, we can strive to be the first to know and fast to market, helping to prevent diseases in animals that could be dangerous to people," said Knupp.

ANIMAL HEALTH EMBRACES TECHNOLOGICAL ADVANCES

Like their Big Pharma counterparts, the major animal health companies have turned to technology to improve the development as well as the application of their products. For example, Merial has designed a vaccine delivery method that "has the potential to transform poultry vaccination practices around the world," said Jerome Baudon, global head of the company's avian business. The vaccine is an effervescent tablet that is dissolved in drinking water, which is then sprayed over a flock of poultry or administered nasally or orally to individual chickens. Merial's vaccine against the highly contagious Newcastle disease virus is the first application of the effervescent delivery technology.

Genomics technology, which has significantly advanced human drug development, also has been embraced in the animal health industry, particularly in livestock breeding. Zoetis scientists designed the first U.S.-based genomic test for the six most common and costly diseases among Holstein cattle. The test results help farmers selectively breed herds with reduced risks of health problems. Similar genetic tests have been designed to improve the breeding of

sheep and Angus cattle.

Animal health companies also have recognized the potential of digital technologies to improve their relationships with customers and promote the health of their respective "patient" populations. Since January 2016, Merial has collaborated with the Georgia Institute of Technology's Center for the Development and Application of Internet of Things Technologies to identify possible ways that networked devices (aka Internet of Things) can advance animal healthcare and wellness.

Zoetis is participating in a 42-month U.K.-based project to develop visual imaging methods and digital technologies that will help farmers improve the health and wellness of pig herds and enhance production efficiency. The $3 million project was funded by Innovate U.K.'s Agri-Tech Catalyst Award. In addition, Zoetis opened a Centre for Digital Innovation in London in 2015. This year, the company and the U.K.'s University of Surrey announced the establishment of the Veterinary Health Innovation Engine (vHive), a novel multidisciplinary center at the university that will promote the development and adoption of digital technologies in animal health, including disease surveillance and early detection.

What's next in the animal health sector? The industry's demand drivers of pet ownership and protein consumption are highly unlikely to change. Corporate changes, however, are expected to continue to influence the industry.

Because of Zoetis' financial success and independence, business journalists often refer to the company as a possible takeover target. In December 2015, Sanofi and Boehringer Ingelheim (BI) announced a $12.5 billion asset swap in which Sanofi will hand over Merial to BI in exchange for the German company's consumer health unit. If the deal is finalized, BI's animal health division will become the second-largest animal health company. Such mergers are not unusual in the animal health sector. In 2015, Eli Lilly's Elanco acquired Novartis' animal health division.

The future of Bayer's animal health division also is uncertain. In April 2016, Reuters reported that Bayer's new CEO, Werner Baumann, is questioning whether the company's animal health division is "well placed with us as best owner or can these businesses perhaps progress better in a different environment, with different access to resources?" L

Move Over ADCs: Nanoparticle-Drug Conjugates Are Joining The Cancer Fight

LOUIS GARGUILO Chief Editor, Outsourced Pharma @louis_garguilo

Just when we were feeling comfortable in our understanding of the science and technologies behind ADCs – drugs linked to antibodies that target tumor cells – we need to plunge into the next advancement in this cancer-fighting realm. Cerulean Pharma (NASDAQ: CERU) President and CEO, Chris Guiffre, at his office within the AstraZeneca BioHub in Waltham, MA, assures me it'll be well worth the dive.

Cerulean's been at this new form of anti-cancer drug development and delivery since 2006. The journey has been anything but straight-line. To help us better understand it all, we're also joined by the inventor of Cerulean's lead drug, and what Cerulean calls this new category of cancer treatment: nanoparticle-drug conjugates (NDCs). Mark Davis, Ph.D., is professor of Chemical Engineering at the California Institute of Technology (Caltech). Davis is in an elite group of individuals who are members of the National Academy of Sciences, the National Academy of Engineering, and the National Academy of Medicine. "A rare triple threat," as Guiffre calls him.

According to both men, NDCs are an evolution of ADCs (antibody-drug conjugates) and a refinement of "old-fashioned nanotechnology." Specifically, Cerulean's goal is to create a cancer treatment that's more efficient, effective, and better tolerated by patients, and thus more humane. (For Davis, this is a personal matter, documented in the sidebar.)

After paddling through some rough waters (described below), Cerulean raised capital via an IPO in the spring of 2014. It's now re-advancing its lead compound — CRLX101 — through a Phase 2 clinical trial soon to wrap up. A subsequent Phase 3 trial could get underway early next year. The company also has follow-on compounds in the clinic. It's developed a platform technology for future biopharma partnerships to create more NDCs. The overall business plan is, of course, contingent upon further progress in the clinic, but if that happens, Cerulean might just propel us into an era of the independent, commercially successful nanopharmaceutical company.

But first ... that science and technology dive.

NANOTECHNOLOGY FLOWS FROM THE SHORES OF ADCs

Guiffre, in his current role as chief executive since March of last year, says that Cerulean created the NDC moniker. "We gave some thought to trademarking the term," he says, "but decided the real value is in it being used to describe a new class of drugs that are a next-generation nanopharmaceutical. We're deter-

WHEN NANOMEDICINE GOT PERSONAL

LOUIS GARGUILO

Documenting everything Mark Davis is and does professionally takes more than a few nano-seconds. Among other things, he's the Warren and Katharine Schlinger professor of Chemical Engineering at the California Institute of Technology and a member of the Comprehensive Cancer Center at the City of Hope and the Jonsson Comprehensive Cancer Center at UCLA. He was the first engineer to win the National Science Foundation Alan T. Waterman Award. He's been elected into the National Academy of Engineering, the National Academy of Sciences, and the National Academy of Medicine.

Most important to us, though, is something personal for Davis: his strong desire to develop a nanopharmaceutical that better targets tumors and thus alleviates the suffering cancer patients encounter with current treatments.

Davis' wife, Mary, was diagnosed with breast cancer at the age of 36 in April 1995. Thankfully, she is a cancer survivor. Davis has written about that time. "By Valentine's Day, Mary had lost all her hair for the second time. She was unable to eat, was constantly vomiting or felt nauseous, and was given nutrition by IV. She had completely lost her immune system and was in isolation for three weeks." During that isolation, Mary said to Davis: "There's got to be a better way … the treatments are making me sick. Treatments should make you feel better." When he replied this was not his field of expertise, she retorted: "You people at Caltech are smart, go work on it."

As we were starting our discussion for our main article on Cerulean, company president and CEO, Chris Guiffre, was adamant that I first understand this dimension that Davis brings to the company. As per that article, Cerulean is attempting to commercialize the drug and nanotechnology developed by Davis to fight cancer. "Mark is a brilliant scientist, and this has been his motivation inspiring his nano inventions in the field of cancer. He decided to invest decades of his life to get to where we are now."

Davis and Cerulean are winding up a Phase 2 clinical trial, with more planned and backup compounds also in the clinic. Professor Davis' nanoparticle-drug conjugates (NDCs) are, according to Guiffre and Davis, the next step in an evolution of "old-fashioned nanotechnology" applied to the theory of antibody-drug conjugates (ADCs), which themselves have been exciting developments in the fight against cancer and specifically better patient experiences during the battle.

Technology For A Humane Cancer Treatment

Here's a bit more detail on the technology Davis and Cerulean are developing, particularly the fundamental attributes – and differences – between ADCs and their NDCs:

- With ADCs, a cytotoxin (anti-cancer agent) is linked to a monoclonal antibody that seeks out and attaches to tumors via overexpressed receptors on the surface of the cancer cells. In theory, the cytotoxin is then released. Unfortunately, during the course of treatment, the state of overexpressed receptors can disappear. There remain limitations on how much cytotoxin (and which ones) can be successfully linked to a certain antibody, and although ADCs help spare healthy tissue by targeting tumors, overall ADC stability and release of the cytotoxin remains problematic.
- With NDCs, a cytotoxin is linked to a nanoparticle, which in the case of Cerulean's technology, actually enters tumors by taking advantage of EPR – enhanced permeability and retention effect. Moreover, once inside – in a process called macropinocytosis – the tumors actively engulf the NDCs. "It's almost as if the tumor consumes the NDC as food," Guiffre says, except of course this food is lethal.

Getting Closer

The drug and technology Cerulean in-licensed from professor Davis, known as CRLX101, has, to date, been tested in more than 350 patients, as both monotherapy and in combination with other cancer treatments. At this writing, we know from multiple clinical trials that CRLX101 is encouragingly active as both monotherapy and those combinations of treatment. Of great personal importance to Davis – and cancer patients – is the drug is well tolerated, and spares healthy tissue.

"I would never have done this without having seen what Mary went through," says Davis.

And according to Guiffre, everyone at Cerulean has taken up his personal goal and Mary's challenge. There will be no lack of motivation to keep moving forward at Cerulean.

mined to see it used even more than ADCs some day."

Regarding those ADCs, Guiffre draws us back about a decade, "when people were raising an eyebrow at the technology, and wondering why Seattle Genetics and Immunogen [leaders in this field] hadn't given up." Instead, they and others started delivering on the promise of targeting tumors and sparing healthy tissue in cancer treatment. Two ADCs are currently marketed: Brentuximab vedotin (Adcetris; Seattle Genetics and Millennium/Takeda) and Trastuzumab emtansine (Kadcyla; Immunogen and Genentech/Roche). Many companies have entered the field in the past few years, including Big Pharmas, such as Merck, Pfizer, and Sanofi. (In previous issues I've also written about nano-specialists such as Nanobiotix, Sonrgy, and Cour.)

The fundamental difference between Cerulean's NDCs and their biology-based predecessors is the replacing of antibodies (biology; living organisms) with particles (nanotechnology; fabricated and shaped organic material) to deliver cancer agents directly to tumors. This alteration of science and material actually allows for the release of highly toxic anti-cancer drugs within a tumor: more potent medicine delivered more safely.

Cerulean's NDCs also improve on other nanotechnologies. Guiffre boils it down for us. "First, due to our nanoparticle 'backbone,' our NDCs remain stable in the bloodstream. They are small enough to slip through the large pores in solid tumor vasculature, but large enough so they don't slip through the small pores in healthy vasculature. Based on our conjugation, they penetrate the tumor tissue until taken up inside the tumor cells, through a process called macropinocytosis. Only then is the drug slowly released, thanks to our linker technology. You can see the advantages of both nanotechnologies and ADCs at work here."

SHAPE AND SIZE MATTER

In what professor Davis describes as a world's first, he and his colleagues published a paper earlier this year in PNAS (*Proceedings of the National Academy of Sciences of the United States of America*) describing a clinical trial of nine patients demonstrating that nanoparticles in human beings do concentrate in tumors and spare adjacent, healthy tissue. "It works as advertised," says Davis.

What "worked" was Cerulean's lead compound, CRLX101. It's an NDC with a payload of camptothecin, a potent chemotherapy discontinued in clinical development in the 1970s because it was too toxic for patients to handle. (There are other camptothecin-class drugs on the market, including irinotecan and topotecan.) By linking camptothecin to the nanoparticle payload, Davis invented a new chemical entity (NCE).

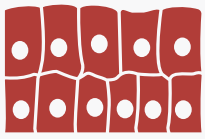
CRLX101's lead indication is relapsed renal cell carcinoma: kidney cancer. The FDA granted CRLX101 fast track designation in combination with Avastin (bevacizumab) for the treatment of metastatic renal cell carcinoma following progression through two or three prior lines of therapy. CRLX101's second indication is platinum-resistant ovarian cancer. The FDA granted CRLX101 orphan-drug designation in this indication.

Why CRLX101 worked is a matter of shape and size. "I've been preaching for a long time for 'well-designed nanoparticles,'" says Davis. He explains that most nanoparticles today don't possess the requisite properties, including the most fundamental attribute of size. Many *Life Science Leader* readers will know the nano field was defined when it became possible to bring particle size down to the magic number of 100 nanometers. Not good enough, says Davis. "We kept saying 100 nanometers is way too large if you actually want particles to penetrate and access the larger part

ADVANTAGES OF NANOMEDICINE

Faster diagnosis of many ailments

More precise treatments of conditions such as cancer



Repair tissue deep within the body

Target only diseased organs without destroying healthy tissue

Source: clinam.org/benefits

> *"We kept saying 100 nanometers is way too large if you actually want particles to penetrate and access the larger part of the tumor. Cerulean's particles are much smaller."*
>
> **MARK DAVIS, PH.D.**
> Professor of Chemical Engineering, Caltech

of the tumor. Cerulean's particles are much smaller, in a range of 30 nanometers, and much better designed. That's being verified now."

Finally, Guiffre brings up the component in drug conjugation that has differentiated, limited, frustrated, and at times otherwise defined the ADC platform from its beginning: the "linker" technology. More precisely, how do you stably "link" a toxic anti-cancer agent to an antibody so that the agent is not released anywhere but at the site of the tumor? As this combining (or conjugation) of payload, linker, and antibody continues to evolve on the ADC side, nanotechnology may be jumping ahead with better options. Guiffre says Cerulean has become adept at nano-linker technology.

"We now have clinical data showing DNA damage in ovarian cancer patients almost a week after a single dose of CRLX101," Guiffre says. "That's really quite remarkable to have that kind of an effect."

COMING UP FOR AIR

Some of that success was arrived at via an unsuccessful clinical trial. It was in 2013, some 10 years after the founding of Cerulean by Alan Crane, the company's first CEO and a partner in Boston-based healthcare firm, Polaris Ventures. CRLX101 failed to reach its endpoint in an initial Phase 2 clinical study in nonsmall cell lung cancer, throwing the company into a flurry of notoriety and adversity.

The trial brought with it some lessons learned the hard way. "That failure in the clinic really had nothing to do with the drug itself," says Guiffre. "It had everything to do with our having poorly designed the study, which we then had conducted in Russia and Ukraine. With the benefit of hindsight, that trial was doomed to failure from the beginning."

Davis and Guiffre, though, point to the ray of enlightenment emanating from that experience. They say in retrospect this was the first randomized study where a large number of patients showed that CRLX101 had similar overall survival, progression-free survival, and overall response rate to FDA-approved cancer drugs in second and third line nonsmall cell lung cancer. "Maybe even more importantly," says Guiffre, "we delivered a highly-toxic drug into 100 cancer patients, and it was remarkably well-tolerated."

Have others — potential investors perhaps — drawn those same positive conclusions from this first defeat in the clinic? "Well," replies Guiffre, "you normally don't write stories about companies that go public with a successful IPO 13 months after having such a failure in a randomized trial. But part of why we are here now is because that trial proved our NDC did what it was supposed to do."

TARGETING CERULEAN'S FUTURE

Four years later, Cerulean's back in the clinic with CRLX101. A second NDC in the Cerulean pipeline, CRLX301, will most likely have started its Phase 2 trial by the time you read this. Cerulean has also developed a full-blown NDC-creating technology, called Dynamic Tumor Targeting Platform. (This time Guiffre has decided to trademark.) The company is banking on this technology to bring in partners and collaborators from the biopharma industry. Guiffre calls these "platform deals." He explains, "This is similar to what Seattle Genetics and Immunogen have done in their ADC history. It took them some time to attract partners. Now it seems like every big biopharmaceutical

"We now have clinical data showing DNA damage in ovarian cancer patients almost a week after a single dose of CRLX101. That's really quite remarkable to have that kind of an effect."

CHRIS GUIFFRE
President and CEO, Cerulean Pharma

company is working with one of those two groundbreaking ADC companies. I think Cerulean is at that point. We've proven our technology, and it's realistic to think we'll engage in these strategic collaborations."

We'll have to wait to see if that enthusiasm, and grand comparison, pans out. As Guiffre indicates, there's nothing unusual about a technology platform, and, in fact, besides in the area of ADCs, contract research and development organizations of various stripes are employing it to gain customers and partners. In Cerulean's case, a drug company would come to them with a potential anti-cancer drug (the NDC payload) with significant activity, but as is too often the case, also with concerns about the therapeutic index (i.e., efficacy versus toxicity). Cerulean could potentially engineer the compound into an NDC for the partner to then take into the clinic. One can envision various revenue models for this beyond pay-for-service, including Cerulean taking a stake in the future success of molecules, milestone payments, and additional technology development. All of these (and more) have been put together on the ADC side.

A second partnership, or contract-service strategy for Cerulean — again not entirely untried — has to do with patent expansion. Guiffre believes his NDC platform will allow biopharmaceutical companies to launch improved products to replace those about to go off patent. "The successor product would become an enhanced NDC, with the original product as its payload, making it safer and more effective, and adding IP," he explains. "Doctors are already familiar with the original product. Now they can offer patients a better version that's more active *and* better tolerated. I ultimately think that's the strategy that will pay significant dividends for us, our partners, and for patients."

NO SMALL PLANS FOR THE FUTURE

The final part of our dive — although accompanied by remaining waves of assumption — is into the future. What's the ultimate game plan for Cerulean should CRLX101 (or other NDCs) gain FDA-approval to treat one or more forms of cancer? Will Cerulean out-license to an established Pharma (or Bio)? Will it opt to become one of the first nano-versions of commercial biotechs?

"If you think of the well-known example of Abraxis, a nanotech company that was acquired by Celgene for about $3 billion, they were on their way to becoming a very successful independent nanotech before they were acquired," says Guiffre. "That certainly is one path that can't be ruled out." Again, we'll credit Guiffre for an expansive and enthusiastic comparison. Yet, somehow I sense even this bright scenario might not be his first choice. In fact, after a pause, he adds another colossal comparison: "However, if we were to launch our products and commercialize them ourselves in the U.S. — as we did when I was at Cubist — could we grow to become the next Biogen or Genzyme in Boston? I hope so. If that happens, I think you may point to us as the first commercial biopharmaceutical company grown entirely on nanotechnology."

As someone who's been following this integration of nanotechnology with drug discovery and development, that would be a grand accomplishment. And I think Guiffre would agree; it never could have been achieved without a great assist from the biopharma pioneers who first brought us, and continue, the science and technology of ADCs. L

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Onboarding: Key To J&J's Long-Term Investment Vision

CINDY DUBIN Contributing Writer

Life sciences observers continue to spot a trend that comes more into focus every year: Big Pharma is reducing investment in its own R&D, yet investment in early-stage venture-funded companies seems to be growing. Big Pharma recognizes that there is a lot of good science going on outside their own walls, and rather than try to start up their own internal programs in all of the spaces they are strategically interested in, it sometimes makes sense to fund those programs externally (for a while) to see how they evolve before, possibly, pursuing an acquisition. This begs the question: Who is funding the future of life science innovation?

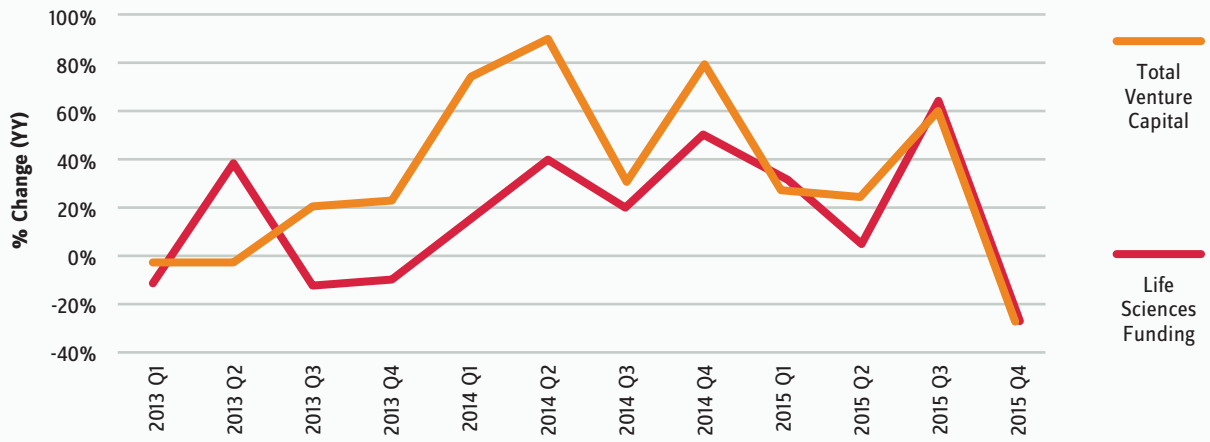
According to the *MoneyTree Report* from PricewaterhouseCoopers (PwC) and the National Venture Capital Association (NVCA), traditional VC firms invested $2 billion in 172 life sciences deals in the fourth quarter of 2015, compared with $2.8 billion in 202 deals during the same quarter of 2014. With $10.1 billion invested in 783 deals for the full year 2015, the life sciences industry was the second-most-invested destination after software, in terms of dollars.

But, Big Pharma's long-term health depends on developing new breakthrough drugs, and three routes to achieving this include in-house R&D, acquiring or in-licensing promising pipeline drugs from other companies, and investing in promising new companies with the hope of acquiring them later. Thus, Big Pharma has stepped in to support early-stage companies alongside their VC counterparts.

Moderna Therapeutics is a prime example. The Cambridge, MA-based company raised $450 million from high-profile partners including Alexion Pharmaceuticals and AstraZeneca in the largest private fundraising round for any biotechnology company on record, according to *Forbes*. The company is developing a novel approach to medicine that leverages messenger RNA to treat cardiovascular, metabolic, and rare diseases.

The leading corporate venture investors in the industry include Novo Nordisk; Novartis; Pfizer; S.R. One (GlaxoSmithKline's independent corporate

LIFE SCIENCES FUNDING COMPARED WITH TOTAL VENTURE FUNDING, 2013-2015



Source: MoneyTree Report from PricewaterhouseCoopers (PwC) LLP and the National Venture Capital Association (NVCA).

"This strategy is atypical, but creating new companies can result in new platforms for us in the future."

TOM HEYMAN
President, Johnson & Johnson Innovation

healthcare venture capital fund); and Johnson & Johnson Innovation-JJDC, Inc (JJDC), previously called Johnson & Johnson Development Corp. In fact, from 2014 to 2015, JJDC was one of the most active VC investors among pharma corporations, investing hundreds of millions of dollars.

JJDC is interested in investing equity in small companies, primarily those in the medical device, pharmaceutical, and consumer sectors. JJDC operates as a subsidiary of J&J and the group responsible for equity investments, including venture investments. JJDC has been around since 1973, which is really when many of the venture firms we see today were forming. The firm specializes in investments from the early stages of seed funding, including startup, early-, mid-, and late-venture investments, to the advanced stages of series venture investment, as well as private investments in public equity (PIPE).

Since March 2000, JJDC has made hundreds of investments in hundreds of companies. JJDC is not unique among corporate VCs in that it is a venture group, but, unlike the others, it is not a financial investor, explains Tom Heyman, president of JJDC and CEO of Janssen Pharmaceutica NV in Belgium. "Many pharmaceutical companies have created venture capital groups, but we are primarily strategic investors, investing in the companies that have tools, technologies, and products that might be of strategic interest to our sectors today or in the future. For us, everything we do has to be a financially sound decision, but it's about strategy first and all else follows," he says.

INVESTMENTS SUPPORT KEY SECTORS

The majority of JJDC's investments have been of interest to specific J&J business units (medical devices, pharma, and consumer products), and most of its investment dollars have funded such deals.

The JJDC group has only nine active investors. Two years ago, four regional innovation centers were formed by J&J, and the majority of the investors were moved to those regions: Menlo Park, Boston, London, and Shanghai. "These innovation centers ensure we are close to where the innovation in our areas of interest is happening," says Heyman.

Together with the innovation center teams and representatives from its business units (e.g., pharmaceutical, consumer, medical device), JJDC investors identify market trends and companies pursuant to the corporation's strategic goals. For example, two years ago, J&J and JJDC decided to enter the microbiome space. The team suggested a company called Vedanta Biosciences.

"We believed Vedanta Biosciences had an interesting science to start our path forward in the microbiome space," says Heyman. Since that time, Vedanta has moved into JLABS in Boston, part of J&J's biotech incubator network. Through JLABS' facilities and satellite locations, companies gain access to move-in-ready modular lab and office space, allowing them to pay for only the space they need and expand quickly when they are ready.

Shortly thereafter, J&J's pharmaceutical business, Janssen, obtained a license to develop and commercialize Vedanta's pharmaceutical candidate in inflammatory bowel disease (IBD). Vedanta received an up-front payment and is eligible to receive development and commercialization milestone payments for an IBD indication up to a potential total of $241 million, plus possible additional consideration related to commercialization.

Another example of JJDC's investor insight is related to a European-based oncology company called Genmab, which was developing a promising treatment for multiple myeloma. "We were in discussions with Genmab for a licensing deal, but it was also important to them that we would make an equity investment as part of the collaboration," explains Heyman. "We used equity as a tool to bring in the licensing deal." That product was approved late last year.

Genmab received an up-front license fee of $55 million, and JJDC invested approximately $80 million for 5.4 million shares of Genmab. The total potential agreement value, including up-front payment, equity investment, and milestones, is in excess of $1.1 billion. Janssen was responsible for the costs of the ongoing development of the asset, which is now approved for use in multiple myeloma patients and is on the market in the U.S.

In seeking breakthrough technologies, JJDC has made a number of new medical device investments in the past year, including a Series A investment in Cala Health. Renee Ryan, VP of investments at JJDC, who works out of J&J's Innovation Center in Menlo Park, said the company was of particular interest to J&J because it is developing a therapeutic wearable device for patients with movement disorders based on

technology developed at Stanford University.

As a complement to its four regional innovation centers and its JLABS incubators in North America, J&J has just launched JLINX, an incubator initiative to support early-stage European companies to pursue research. JLINX, a collaboration with Janssen Pharmaceutica NV, will offer scientists and entrepreneurs access to venture funding from JJDC, R&D expertise, and state-of-the-art facilities. "JLINX fits in Johnson & Johnson's overall external innovation strategy and fits with JJDC's strategy as well," says Heyman.

VALUE-ADDED INVESTING

No matter what the investment, there obviously needs to be a value to both sides. "In the end, the company should be one that we want to bring on board, either as a corporation or through a strategic transaction," says Heyman. "That is how we create value for J&J. It's not necessarily the equity investment that creates value, it's the onboarding of an asset that creates value because it will add to the pipeline we have in our medical device, consumer, or pharmaceutical groups."

JJDC also brings value to the company in which it is investing by helping address issues related to R&D or commercialization. "If we help solve their problems, we have a better chance of onboarding the asset down the road for J&J, and by doing that, we create value for J&J," he says. "Sure, the financial part is important, but we are happier if the investment creates a situation where the company or asset becomes part of J&J or we obtain a licensing deal or form a collaboration."

Strategic onboarding is an important part of JJDC's strategy, and while the exact frequency varies, about every 18 months or so, one of JJDC's portfolio companies gets onboarded by J&J. "This can get tricky, because we are often invested in companies that have multiple programs being developed in parallel, but we may want to onboard only one of those assets," says Ryan. "In those instances, we in-license the one program into our pipeline, and JJDC remains an investor since we still hold equity in that company."

Heyman adds, "To me, if we want to make equity investments, the end goal is onboarding the company. While lots of things can happen along the way to a company that might prevent that, such as technology or clinical failures, I define success as onboarding a company. We work closely with our sector teams on the decision to onboard or not, but ultimately the decision is theirs."

Going forward, Heyman wants JJDC to be more proactive when using equity to create new companies based on technology J&J has acquired or has in house. "This strategy is atypical, but creating new companies can result in new platforms for us in the future, and we need to take a long-term view with respect to company creation." L

VENTURE CAPITAL AND CORPORATE VENTURE ACCELERATE INVESTING PACE

Most Active* New VC Investors in Biopharma 2014-2015: Venture Capital and Corporate Venture Capital

TOP VC BIOPHARMA

INVESTOR	DEALS	TOTAL $
OrbiMed Advisors	30	$1,300M
Novo	20	$736M
NEA	19	$713M
Versant Ventures	16	$376M
Sofinnova Ventures	15	$742M
Fidelity Biosciences	12	$586M
Venrock	11	$705M
ARCH Venture Partners	11	$630M
MPM Capital	10	$236M
Atlas Venture	10	$143M

TOP CVC BIOPHARMA

INVESTOR	DEALS	TOTAL $
JJDC	18	$235M
Novartis Venture Funds	13	$321M
SR One	11	$305M
Pfizer Venture Investments	9	$221M
Celgene	8	$260M
WuXi Venture Fund	8	$204M
Roche Venture Fund	7	$198M
Lilly Ventures	7	$106M
Partners HealthCare Innovation	7	$104M
GlaxoSmithKline	6	$92M

Of the top venture capital investors, three (OrbiMed, Sofinnova, Venrock) joined crossover syndicate partners in at least 50 percent of their 2015 new deals.

Top biopharma investor OrbiMed Advisors raised a $950M fund in late 2015, and it's likely to remain very active.

WuXi Venture Fund separated from its corporate parent and in Q4 raised a traditional venture fund.

GlaxoSmithKline appears on the CVC list twice: For its corporate venture arm (SR One) and for its early-stage parent company investments, many of which are with Avalon Ventures.

**Most active defined as top 60 investors based on new investments*
Source: CB Insights, press release, PitchBook and SVB proprietary data

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HUYA: *Leveraging China Innovation For Worldwide Growth*

ED MISETA Chief Editor, Clinical Leader @EdClinical

DR. MIREILLE GILLINGS
Founder and Executive Chair,
HUYA Bioscience International

When you talk to Dr. Mireille Gillings, the founder and executive chair of HUYA Bioscience International, her enthusiasm and passion for drug development is clearly evident. During our discussion, Gillings explained why she believes her company has a unique business model that can reduce the risk of drug failure and development time as well as the cost to get a new drug to patients. By tapping into medicinal discoveries taking place in China, she is able to in-license the innovative candidates and develop them outside of China in the U.S., Europe, or the rest of Asia.

"HUYA performs discovery differently by not having the bricks and mortar and related overhead that go with it," she says. "Instead, we work with innovators who are located in China. Many of these researchers, called 'sea turtles', were educated in American and European universities but returned to China to conduct their research and development in their native country."

Innovative R&D in life sciences has been gaining momentum in the East, and China is currently leading the way as it supports research with government funding while also placing a high value on innovation. From the very beginning, Gillings had a vision of adding value to the wealth of therapeutic opportunities under development in Chinese institutes and universities. HUYA identifies the most promising preclinical and clinical stage compounds for licensing and then leverages and extends the research efforts of those partners. In doing so, the company provides a bridge to development efforts in global markets. All of the candidate compounds are evaluated through a rigorous process in China by HUYA. More importantly, the company's relationship with Chinese partners provides HUYA with an ever-increasing continuous source of compounds for the future.

Overcoming Regulatory Hurdles

HUYA focuses on oncology and cardiovascular disease. In the oncology space, the company already has two licensed programs in development. For the lead program, HUYA met with the FDA for a pre-IND (investigational new drug) meeting, and the agency agreed to accept the data provided by Chinese researchers.

Gillings also has had success in leveraging the

Trilateral Cooperation Secretariat, an agreement signed in 2004 between China, Korea, and Japan to promote cooperation among the major countries in Asia. A key part of the agreement addresses each country's different requirements for regulatory approval of clinical trials and new drugs. In China, for example, it can take longer to get a compound into the clinic. "This reflects the larger preclinical data package the CFDA (China Food and Drug Administration) requires before approving the start of clinical testing," notes Gillings. "In the U.S., we have the opposite situation in that toxicology studies, for example, are generally less involved and less time-consuming than they are in China."

The Trilateral agreement circumvents these differences by allowing research data from one country to be shared among the three nations. This shortens the regulatory timeframe for getting a compound into a clinical trial in a partner country, since data no longer needs to be duplicated in another country to gain regulatory approval to proceed into clinical testing.

According to Gillings, HUYA was the first company to leverage the Trilateral agreement. The company took Chinese data involving HUYA's lead oncology compound called HBI-8000 and presented it to the Pharmaceuticals and Medical Devices Agency (PMDA), which is part of the Japan Association for the Advancement of Medical Equipment (JAAME).

"After seeing the clinical data from China for the treatment of lymphoma, the PMDA gave us an accelerated development path forward," states Gillings.

The result is that HBI-8000 is now about to enter a trial designed for approval in lymphoma in Japan while it is also in development in the U.S. for additional indications in oncology.

The Importance of "Scouts"

Gillings founded HUYA Bioscience 10 years ago and initially spent 80 percent of her time in China building relationships. Working alone, she reached out to as many innovators and researchers as possible across the country. Her primary goal was to locate potential partners and learn about projects they had underway.

"Because science is an international language, I was able to have meaningful conversations that enabled me to recognize innovative compounds that had the potential to become successful drugs," she says. "All that legwork created an effective network that ultimately allowed the company to create a database that now includes more than 14,000 compounds. Today, this accounts for access to approximately 55 percent of the drug innovation currently in China. HUYA's operations have grown and are now supported by the eight offices in China, including Beijing and Shanghai."

The company has close to 100 employees in China that Gillings refers to as "scouts," who tend to be PhDs and medical doctors (90 percent of scouts have advanced degrees) and who are responsible for locating the compounds that will result in HUYA's future success. "Our scouts essentially expand on what I did initially when the company began," notes Gillings. "They build individual relationships with scientists in China by talking about science one-on-one with the innovators." The scouts have helped HUYA establish 114 "first-look" agreements with top-tier institutes and universities, giving the company first access to any innovative compounds in development.

Gillings generally looks for compounds that are IND-ready and about to enter a Phase 1 trial, preferring drugs that are at an earlier stage of development. By in-licensing such candidates, the company acquires rights to the products for global development. For a compound like HBI-8000, HUYA owns the worldwide rights outside of China. This means that the university, institution, or biotech company that discovered the compound retains development rights in China, allowing them to retain the value created within their country.

Gillings adds that the relationship doesn't end with in-licensing. HUYA continues to collaborate with the innovators developing their compounds in China by providing valuable guidance that helps advance drug development. In fact, HUYA has an in-house development team that includes multiple international advisors with expertise spanning all aspects of drug development and commercialization. It also has preferred CROs that it works closely with globally, enabling HUYA to operate more virtually and with less investment of time and money than a traditional pharma model. "We maintain control over development and are intimately involved with the design and oversight of each clinical trial," explains Gillings. "Most of our preclinical work is done with Charles River Labs, while the clinical trials are performed by Quintiles."

Knowledgeable Employees Are A Key Component

Today, HUYA has grown to nearly 150 employees, although with advisors and consultants, it has human resources totaling more than 200 people worldwide.

In addition, the company has become so well-known in China that researchers often reach out to HUYA before scouts make contact. However, this hasn't changed the company's review process. When an interesting compound is identified, the accumulated data package goes to the team in San Diego where another group of PhDs and MDs thoroughly review it. Ultimately, the strength of the data, market potential, and intellectual property are all considered when selecting products that have the desired profile for licensing.

Even when HUYA is presented with opportunities that are too early to in-license, the company still interacts with the innovators, advising them on how to best advance their candidates in development until the time is right to re-engage in licensing discussions.

Obviously the researchers and scouts at HUYA have

to be well-trained in the drug discovery process. A single misstep in analyzing the compound, the data, or the market for the product can be costly to the company. For that reason, the team in China is made up of individuals who have experience in pharma and, specifically, clinical trials. "We have drug developers and bench scientists who help with all aspects of preclinical development," states Gillings. "Many of our employees have previously worked for international pharmaceutical companies, and, therefore, they bring a valuable global development experience and perspective to China."

She adds that the scouts need to understand the commercial aspects of the pharmaceutical industry, not just technology. Even if a drug candidate looks promising at an early stage, it doesn't necessarily translate into future commercial success. "The market potential for a compound is as important as the science," says Gillings. "We need answers to the following questions when making our assessments:

- Are there are similar drugs on the market?
- Is there anything similar being advanced in pharma's pipeline?
- What is the size of the market?
- Will we be able to protect our IP?
- Can the drug be produced via CMC (chemistry, manufacturing, and controls)?

All of this is hard to predict when the drug is seven, 10, or 12 years away from approval."

To answer these questions, HUYA's international team has to work closely together, which means proper communication is essential. Thus, video conference calls take place every other day involving personnel in the U.S., China, Japan, and South Korea.

Different Paths Lead To International Scale

After the in-licensing process is completed, innovators continue to work on their compounds in China while HUYA pursues a course to approval outside China. The two paths may be similar, or they may pursue entirely different endpoints or even indications. Gillings sees this as a great benefit of the relationship. "Our mutual efforts become complementary as HUYA advances development globally to the benefit of the drug's future within China," she says. "This means innovation can reach an international scale through our partnerships."

The data gathered and shared by both entities is a time and cost saving for the partners. For example, if HUYA's partner in China has data on dosing requirements, those tests do not necessarily have to be replicated by HUYA. "If you don't have to test five or 10 different doses because you know which one works, that saves you time and money since you replicate the doses that work," she adds.

> *"Other companies, and especially Big Pharma, will have difficulty duplicating the HUYA model because it takes time, dedication, and individual attention."*
>
> **DR. MIREILLE GILLINGS**

HUYA is prepared to take molecules right up through to FDA approval, but Gillings notes she would also be open to a Big Pharma company coming in and purchasing a compound her company is developing. In fact, the company recently executed one of the largest deals for a single oncology product in Japan with Eisai Co. Ltd. totaling $280M USD in milestones in addition to royalty payments.

A Model Difficult To Duplicate

When Gillings started the company, industry professionals seemed skeptical about looking for promising pharmaceutical products in China. Today, Chinese innovators have taken notice of the validation of HUYA's business model.

Although more companies are now trying to source products from China, Gillings is confident that her first-mover advantage will keep HUYA ahead of the pack. The company's one-on-one relationships with investigators across China take effort to maintain even with a large team. "Consequently, other companies, and especially Big Pharma, will have difficulty duplicating the HUYA model because it takes time, dedication, and individual attention," says Gillings. "But the competition tells me we're doing all the right things."

She thinks the future looks bright with four compounds in development and a database with molecules covering 17 therapeutic areas, including oncology, central nervous system, metabolic, cardiovascular, and ophthalmologic diseases. Discussions are in various stages with innovators in all of those areas.

"My vision started with a simple desire to help patients, and it has grown into a more sophisticated strategy for accelerating the development of pharmaceutical innovation from China on a global scale. I believe we're making a difference but will have to do even more in the future," she concludes.

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The Changing Role Of The Pharma CIO

GAIL DUTTON Contributing Writer @GailLDutton

"Companies that recognize the opportunities associated with digital transformation are more likely to bring in fresh blood," Murray Aitken, executive director, IMS Institute, says.

To that point, half of biopharma CIOs have been in their current job less than three years, and 70 percent less than five years, according to a recent IMS Health survey. For those CIOs, they understand — and often desire — that this position goes well beyond any traditional responsibilities associated with developing and maintaining information technology and computer systems. Instead, this new breed of CIO helps to add strategic value that shapes the direction of their organizations.

VISION AND LEADERSHIP ARE TOP CIO ATTRIBUTES

"Technology is a cornerstone for the CIO. But for the CIO to be a cornerstone for the business, that person must have the skills to influence and motivate people in a variety of ways to drive the business forward," says Alain Serhan, core leader of digital health initiative for the executive search and advisory firm Egon Zehnder. To access those skills, the CEO and CIO need to talk more about the company's future and how the CIO can help shape that future than about IT itself. This means that vision and leadership are at least as, if not more, valuable than technical skills for the CIO. As Mike Gammons, CIO at Sucampo, points out, "The last CIO I worked for was a leader but not a technology person. She built an efficient, multinational technology group. Technical decisions, however, were largely left to those with more extensive technical knowledge."

Gammons' former company had the luxury of specialization. That CIO focused on developing an IT vision and managing the change necessary to get there. Sucampo, as a smaller company, lacks that luxury. In addition to being a visionary and change manager, Gammons also must be a technology expert.

CUSTOMERS ARE TOP-OF-MIND FOR CIOs

Forward-thinking CEOs, according to the IMS survey, are seeking CIOs who are consumer-centric, digitally fluent, understand data, adaptable, and able and willing to lead change.

One of the biggest mind-set changes is the transition from technology-centric to customer-centric roles, Gammons says, "The CIO function originated because the organization needed someone to make all the devices in an enterprise work together. Now we're focusing on identifying business problems that can be solved with technology."

The recent IMS survey supports that observation. "A transformation is underway," Aitken says. "The CIO is transitioning from someone who keeps the IT infrastructure running to someone who is attuned to the company and thinks about technological solutions to meet current and future challenges." While this trend affects CIOs in all industries, its impact on life sciences is profound. Life sciences finally are implementing IT best practices from other industries such as the use of cloud computing and hybrid cloud and private computing environments, software as a service (SaaS), and platform as a service (PaaS), catalyzed by the increasing complexity of bringing clinical developments to the marketplace at a time when payers, providers, and regulators all seek evidence of real-world efficacy.

"When CIOs asked large pharma R&D heads how they could help, they generally were told they couldn't."

MURRAY AITKEN
Executive director, IMS Institute

"This environment expands CIOs' opportunities to shape the way information is accessed and applied throughout their companies," Aitken points out. "For example, the ability to mine complex datasets from health plans and health records enables companies to study data and develop insights into how patients actually use and respond to specific medications outside of clinical trials."

Those insights are valued by researchers as well as by drug marketers. "Managing that information and making it accessible across functions throughout the enterprise, while preserving its timeliness, integrity, and patient privacy, is the role of the CIO," Aitken says.

OTHER "CHIEF" ROLES COMPETE FOR DOMINANCE

Although innovative CIOs are leading the digital transformation, others are being outmaneuvered. Individual business units trying to maintain control over information and speed of access are creating their own IT experts.

That counters the overall trend in IT toward curating a single source of truth that is kept up-to-date in real or near-real time and used by multiple departments for varying purposes. The return to siloed data risks fragmenting information and causing inefficiencies as business functions struggle with conflicting or inaccessible information.

The proliferation of chief digital officers, chief security officers, chief innovation officers, and other chiefs also dilutes the authority of the CIO over information. "How the development of additional 'chief' roles ultimately affects the CIO role depends on who is in the CIO role and how much opportunity the CIO seizes," Aitken says.

Serhan suggests these ancillary chief roles are stopgap measures while the business units become more attuned to the new digital realities. "In 10 years, organizations will have evolved so there will be no need for such titles as chief digital marketing officer."

Kim Green, chief information security officer for Zephyr Health (a Big Data analytics firm), sees multiple data chiefs as a natural step in companies' digital transformation. "I believe we will continue to see new roles in technology leadership, driven by evolutions in various industries."

Zephyr, for instance, doesn't have a CIO. Instead, its chief security and privacy officer and its VP of engineering jointly address the company's information needs. Green considers this collaboration an integral part of product design, development, and delivery. "Building these concepts [of data security and access] into your product is one of the greatest values leaders in these roles can bring."

CIOs BRING STRATEGIC VALUE

Regardless of how the IT leadership is structured, its strategic value is based upon the ability to provide access to information on a global scale. That requires strengthening their business understanding so they know the goals of each business unit and how those entities actually work, as well as enhancing their own technical knowledge so they are current regarding new and emerging technologies that may present new business opportunities for their organizations.

Deploying predictive analytics is one example. Companies using some of the newest analytics applications can better position their drugs by using data to identify buyers most amenable to new products, those with relationships with competitors, and current and future thought leaders. Big data analytics, predictive analytics, and cloud computing are integral to supplying new levels of information. Yet, despite successes in aerospace and other industries, they are just starting to penetrate life sciences companies. IT industry trade journals cover these topics extensively, as well as trade associations like AFCOM (formerly the Association for Computer Operations Management) and conferences like Data Center World.

CLOUD-SAVVY CIOs SEIZE OPPORTUNITIES

"Life sciences companies are adopting the cloud now," says Michael Hughes, CIO, Anacor Pharmaceuticals. Typically, companies first migrate their application test beds to the cloud, followed by email and storage. Once those are functionally successful, they may migrate

applications and eventually the IT infrastructure (servers, switches, and other hardware) to the cloud.

Cloud adoption typically is the first step toward other IT innovations. The ability to hand off certain tasks to cloud hosts is particularly important for small companies that lack large IT staffs and resources. When Hughes was at Kythera Biopharmaceuticals (since acquired by Allergan), "I moved the entire IT operation to the cloud. Our cloud host had more robust security safeguards than most small companies could provide."

Sucampo's Gammons has migrated 40 percent of the company's IT operations to the cloud, including antivirus software and, soon, storage and email. He says cloud computing allows managers to rethink implementations like enterprise resource planning (ERP) and finance systems, using new technology to cut implementation and reporting times, in some cases, in half.

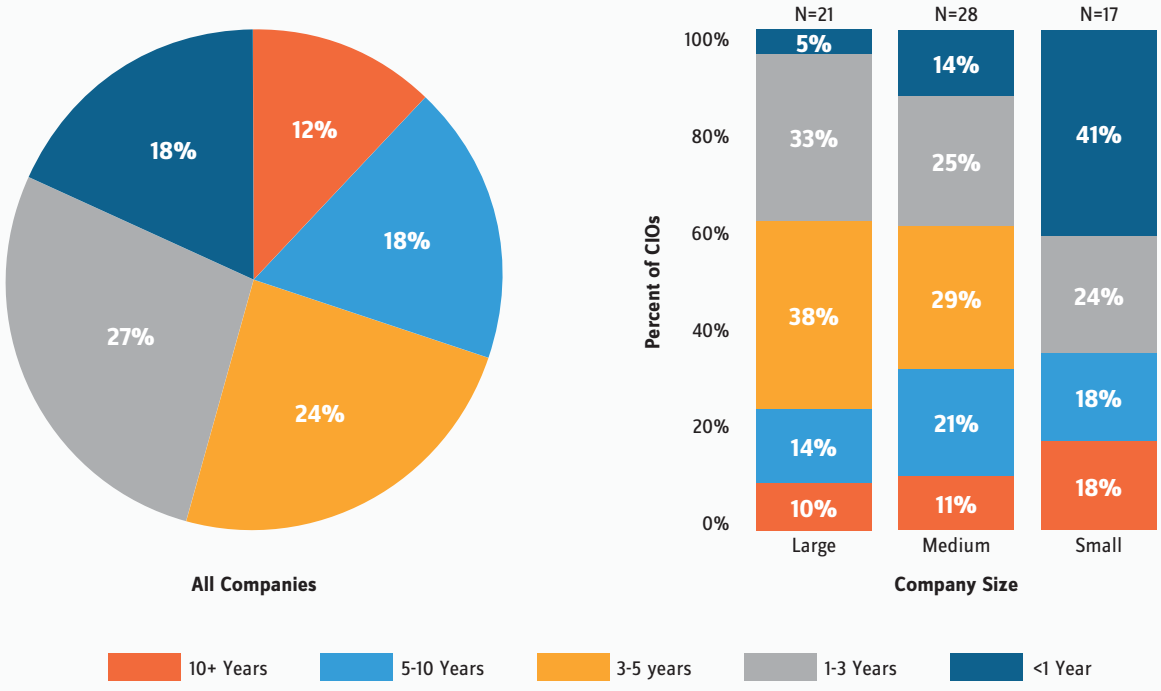
The immediate benefit is increased agility. IT shops free up time by handing off to cloud providers tasks that otherwise would be performed in-house. That extra time may be used to review and update policies and procedures to reflect new working arrangements and IT infrastructure, for example. This also helps CIOs think strategically, becoming more proactive.

Predictive analytics is still in its pioneering phase, used by less than 10 percent of companies in the IMS survey. When deployed, these systems can provide extremely granular views of existing data for accurate real-world insights into compliance, personalized cost-benefit analyses, and other issues. "The role of the CIO is to enable that value to be unlocked," Aitken stresses.

OTHER INDUSTRY EXPERIENCE SPURS INNOVATION

As the CIOs begin to think about technology in terms of how it can help their organizations advance, they are more likely to adopt current and emerging technologies. While a strict regulatory environment often is blamed for the stodgy pharmaceutical IT environment, Hughes, who came to biotech from NASA's Jet Propulsion Laboratory, says that's not the whole story. "Other industries are just as heavily regulated, but their IT departments are innovative." He blames the inertia on researchers and executives

LIFE SCIENCES CIO TENURE AT THEIR CURRENT COMPANY



Source: IMS Institute for Healthcare Informatics, CIO Profiles Analysis, October 2015; IMS Health, MIDAS, June 2015

"Other industries are just as heavily regulated, but their IT departments are innovative."

MICHAEL HUGHES
CIO, Anacor Pharmaceuticals

who've become comfortable with the status quo.

For example, traditionally, pharmaceutical companies were insular, preferring to hire CIOs with deep pharmaceutical experience. Now that's changing.

The IMS survey shows that about two-thirds of life science CIOs have experience in other industries. Consequently, they are bringing the risk-reduction strategies they've used in aerospace, finance, and other regulated industries to their current positions. By implementing those best practices and adapting them to the biopharmaceutical industry, they are crafting innovative IT systems that meet the life sciences' rigorous audit requirements.

Hughes himself is a case in point. Based on his multi-industry insights on the relative values of risk and innovation, he took a chance on a new cloud provider. Consequently, Kythera became one of Veeva Vault's first customers.

WHAT CEOs WANT

While innovative CEOs are embracing digital opportunities, many others are still figuring them out. "CEOs don't know what to ask from IT in this new digital world," Serhan notes. Too often, they think about IT in terms of siloed functions like R&D analytics or, enterprise-wide, as a service provider. CIOs, therefore, need to become more relevant to the core organization.

The problem isn't limited to CEOs. "When CIOs asked large pharma R&D heads how they could help, they generally were told they couldn't," Aitken says. Business unit leaders don't understand IT's capabilities and don't know what to ask to learn.

Yet, CIOs are uniquely equipped to bridge the technology-pharma gap and help their companies develop the most advanced R&D organizations in the world. As the IMS survey shows, 66 percent of the CIOs have advanced degrees, including 43 percent with MBAs.

To bridge that gap effectively, CIOs must become proactive. They must develop relationships with business unit leaders so they understand their challenges and their goals. "The more complex the challenge, the earlier CIOs should be involved," Aitken says. "They should be integral to their organization's development."

Maximizing these new prospects requires CIOs to embrace a culture of change and to identify and seize opportunities. They also must develop horizontal efficiencies across the enterprise.

"CIOs have tremendous influence in companies. It's important they continue to provide core strategic and transformational leadership that supports new business models and creates speedier, more secure paths to market for their products," Green says. Simultaneously, "CIOs must help manage acquisitions and the aggregation of new data sources within an IT system that enhances business continuity and minimizes business risks."

JOINING THE C-SUITE IS IRRELEVANT … OR IS IT?

While many suggest the CIO should be part of the senior management team, that premise is open to debate. Currently, less than 25 percent of CIOs are members of the executive team, the IMS survey reports.

"I'm not convinced the C-suite is appropriate for the CIO," Gammons says. "A lot happens there that shouldn't involve the CIO." Instead, he suggests CIOs are better focusing on their specific areas of expertise.

"Our natural role is to apply enterprise-level thinking to solve the challenges of the functional areas' business problems. Rather than serving in the C-suite, I have independent relations with each member of the management team and report periodically to the board," he says.

Aitken, however, sees value in inclusion. "With the increased flow of more complex data, CIOs may play a more central role that drives organizational change. We at IMS argue that the CIO role is of sufficient strategic importance to be a part of the executive leadership. If it isn't, this is a sign the company isn't fully embracing digital transformation or that the CIO isn't seizing the existing opportunities."

As digital capabilities and possibilities increase, so will the need for comprehensive, enterprise-wide data management. Consequently, Aitken predicts, "The CIO role will continue to grow in importance."

How Do Patients View Your Investigational Medicinal Products?

ED MISETA Chief Editor, Clinical Leader @EdClinical

In early 2013, an initial groundbreaking survey was conducted to determine patient perspectives on investigational medicinal products (IMPs). The survey, sponsored by ISPE (International Society for Pharmaceutical Engineering), was intended to provide an international perspective on IMPs to ensure clinical supply packaging, labels, and booklet labels were patient-friendly.

Unfortunately, 97 percent of the 1,400 respondents were based in the U.S. Additional surveys were conducted in 2015 to garner a more global perspective and include more patients from the EU, China, and Japan.

Esther Sadler-Williams, global director of strategic development and innovation, clinical supply services for Catalent Pharma Solutions, did not want to have to go back to the funders of the original study to ask for more money to complete the EU survey. This necessitated coming up with a creative and inexpensive method of gathering additional data. In the EU, her group worked closely with the NIHR (National Institute for Health Research), which helped along with NHS Greater Glasgow and Clyde, to coordinate the effort with a U.K. network of clinical trial pharmacists.

"The NIHR was a good partner to have," she states. "They worked very hard to grant us access to clinical sites, which then provided us with access to patients. Initially, we were not sure if that would allow us to cast a wide enough net, so we also partnered with EUPATI [European Patients' Academy on Therapeutic Innovation], an organization that really supports patient advocacy groups to try and help them support the clinical trial process."

While those networks gave the researchers the European connections they needed, the group still needed someone to analyze the EU results. That need was met via a partnership with the Biostatics Group of the University of Glasgow. With all of those European partners in place, Sadler-Williams felt it would be possible to pursue the EU survey without going back to underwriters for additional financial support.

The 2013 survey was edited and revised. Questions that provided relevant information were retained, while others were discarded. Other questions were added at the request of the partners. The new survey, which contained 48 questions, was then shared with the research teams in China and Japan.

"We all used the same survey because one of our goals was to be able to look at commonalities across the three regions," says Sadler-Williams. "In Europe, the survey was available only in English. While the surveys were not exactly the same across all three regions, we did try our best to make them as consistent as possible."

EXTRA EFFORT REQUIRED IN CHINA

Lynn Wang, regional lead of Asia Pacific Global Clinical Supply at Merck, headed up the survey in China. She notes a survey of this type, which looked at patient perceptions of clinical supplies, had never been conducted in China. With the number of clinical trials in China increasing during the last 10 years, she also felt the timing was good to take a look at the perspectives of both patients and sites regarding their clinical supplies.

"We took the survey that was prepared by Esther and her team in the EU, translated it into Chinese, and made it available in both paper and mobile versions," says Wang. "This was very different from Europe, where all of the surveys were electronic. We felt that execution would be a primary issue for the patients and wanted to make it as easy as possible for them to complete it. We did have to make some small modifications to it in order to make it more tailored to China researchers and patients. In the U.S. and the EU, many patients may have been involved in clinical research for years, whereas in China, many would have been relatively new to the process."

It was also felt that simply sending patients the paper or mobile survey would not be enough to garner a significant number of responses. In fact, the research team in China took the extra step of contacting participants individually. Questions were handed to the participants, who then had the questions and the intentions of the researchers explained to them. Volunteers also were asked to confirm that they understood the questions and the purpose of the survey.

Reaching out to potential participants was one of the biggest challenges, and various methods were used. Two of the most successful techniques involved community outreach under DIA (Drug Information Association) China and the five organizations that managed clinical sites. A total of 2,500 patient responses was received, with 1,935 containing valid responses. Those were used in the final analysis.

"In the EU, we knew we were at a bit of a disadvantage since the survey was going to be available only in English," says Sadler-Williams. "But before we decided if additional work would have to be undertaken with EU translated versions, we still wanted to see what sort of response we could get and whether the results would be consistent with those obtained in 2013. Japan has initiated a patient survey, but there are a number of challenges in undertaking this type of survey there, so it may be many months before a response that is statistically evaluable can be completed in this region."

SATISFACTION HIGH, BUT IMPROVEMENT OPPORTUNITIES EXIST

First, a recap of the results from the 2013 survey. As noted earlier, 97 percent of those surveys were from U.S. respondents. The survey found a high level of satisfaction with both clinical trial packaging and instructions and an acceptable level of reported compliance. Opportunities for improvement were noted in relation to medicine kit format preferences and kit differentiation, and it was felt new technology solutions could enhance dosing and visits via electronic reminders. Additionally, respondents felt kit design and labeling could play a stronger role in assisting patients with dosing information and proper product handling.

For the patients in Europe and China, one of the key questions on the survey dealt with how easy the clinical medicine kits were to use. The results were similar to the 2013 survey. About 90 percent of respondents found the kits easy or somewhat easy to use. However Sadler-Williams cautions the results should not make pharma complacent, thinking they don't need to change anything. After all, there are still a lot of patients who feel that the kits could be easier to use. "[Not fully understanding the kits] could result in those patients being unable to comply with their dosing schedule," she says. "To illustrate that even further, another question asked if the design of the kit supported the patients' ability to take their medicine on schedule. On this question, the results from the EU and China were very different from the results in the U.S."

Forty percent of respondents in the EU noted the kits helped them to take their medicines on schedule. It was slightly higher (46 percent) in China. However, both of those numbers were significantly less than the 60 percent figure noted in the U.S. So while the majority of patients found the kits easy, or somewhat easy, to use, many found the kit design did not help to remind them to take their medicine.

"I think that is a key takeaway for executives," says Sadler-Williams. "There is an opportunity here to really think about the design of the kit, where possible, and get patient groups together in advance of the study. Present a template of the design and solicit feedback from them. Asking these questions of patients after the trial is too late. Any feedback they provide ahead of time can make the kits easier to use and perhaps improve patient retention."

Wang notes that another key difference that surfaced between U.S./EU respondents and those in China had to do with how patients were notified of dosing instructions. In the EU, 81 percent of respondents (58 percent in the U.S.) indicated dosing instructions on the label would help them to take their medicine on schedule. Another 68 percent noted dosing units on the container would help. In China, only 55 percent felt dosing instructions on the label would help. A significant majority of respondents (77 percent) indicated they would prefer verbal instructions from their physician/nurse/pharmacist on every visit.

"Patients in China clearly prefer that personal communication," says Wang. "Having the information on the label to refer back to is important to patients, but there is still a strong preference for actually hearing those verbal instructions on how and when to take the medicines from the site staff. They enjoyed getting the kit and reading the instructions, but they still wanted to talk to somebody and have it verbally explained to them. That investigator's message is both important and effective."

KIT SIZE AND STORAGE WERE NOT AN ISSUE

Since patients generally have to move and store the kits containing their medicines, you might expect the size of the kits and the ability to properly store them to be important issues for patients. Surprisingly, that was not the case with most patients. In the U.S. study, 77 percent indicated the size of the kits was about right, and 82 percent noted they were easy to store. Similar results came out in the EU and China studies as well.

"Storing the kits wasn't a particular problem to any of the survey participants," notes Sadler-Williams. "Significant majorities in both the EU and China indicated kits were the right size and they were easy, or very easy, to store. When asked what characteristics about the kit were important to them, size and weight (along with single doses) were perceived to be less important, while clear instructions, ease of use, and label information again garnered high marks. Ease of transport was also cited as being a concern."

The researchers were concerned not just about preferences today, but also what they might be in the future. One question asked how patients would prefer to receive information going forward. Here, the responses seemed to vary by region. In the U.S., the top three choices, in order, were text message, smartphone app, and website. In the EU, the order of preference was email, text, and smartphone. In China, the preferred methods were text message, regular mail, and smartphone. The least-preferred method in all three regions was electronic reader.

"This obviously has a lot to do with culture," states Wang. "When you look at the responses from China, two-thirds came from current patients, who were already participating in a clinical trial. The age group also ranged from 54 to 65. This might explain the reluctance to receive messages via email and eReaders (the bottom two choices), but those preferences may change over time."

A PREFERENCE FOR HOME DELIVERY AND RETURNING MEDICINES

A few additional findings are worth noting. Respondents in both the EU and China (approximately 14 percent) indicated they would keep unused medications for future use. In China, only 2 percent of patients said they did not return the used/unused medicines, and 6 percent indicated they would do so occasionally, which is less than that in the U.S. and EU.

Patients were also asked about their preference for having their clinical medicine supplies delivered to their homes, as opposed to having to pick them up at a clinic. In the EU, 71 percent of respondents indicated it would be helpful. In China, 78 percent indicated that option would be very, or somewhat, helpful. While this was expected in older age groups, it was also evident in the younger age groups where patients might have jobs, families, and more active lifestyles.

"Having the information on the label to refer back to is important to patients, but there is still a strong preference for actually hearing .... verbal instructions."

LYNN WANG
Regional lead of Asia Pacific Global Clinical Supply, Merck

"If even a few patients keep their clinical medicines for future use, that is a concern," says Sadler-Williams. "As an industry designing these studies, we need to ensure processes are put in place for sites and patients to understand that all unused medicines are to be returned to the site. Sponsors and sites really need to work harder to make sure all of these medicines are properly returned."

Respondents were also asked about the effectiveness of product labels and pictograms. In the EU, most respondents report having read the booklet label at least once, and most noted it was easy to view and was large enough to read. Ninety-six percent correctly identified the four pictograms that were included. For future use, 51 percent said they would prefer just the text, 8 percent would prefer just the pictogram, and 41 percent would like to see both.

Finally, Sadler-Williams and Wang both recommend that sponsors consider regional differences when designing trials. Even small differences in preference across regions can impact trial results. For example, patients in the U.S. and China have a strong preference for receiving their medicines in bottles, whereas patients in the EU prefer blister packs.

"In large, global studies, we are often tempted to make and manage everything exactly the same," says Sadler-Williams. "This can make things much easier to manage. But what is more important is the preference of the patient. Taking those concerns into account is vital to ensuring the overall success of the trial." L

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5 Fundamentals For Becoming An Exemplary Leader

JIM KOUZES AND BARRY POSNER

Leadership potential is everywhere. And yet, organizations report they have major concerns about the lack of leadership bench strength. Why is this? It's definitely not because there aren't enough people capable of leading. In fact, our global research shows that only one person in a million lacks the skills to lead. What's holding back too many people is a host of inhibiting assumptions, organizational practices that foster environments unsuitable for and inhospitable to growth, and the failure to make leadership development a daily habit.

Leadership is a set of skills, abilities, and attitudes that are learnable. Leadership is not a talent. Nor is it a strength, a position, a gene, a birthright, or something that some people have and others don't. We find it at all levels, among men and women, young and old, in all countries, all ethnic groups. Leadership practices associated with exemplary leadership are universal and within the capacity of nearly everyone to learn. Clearly, learning is the master skill.

You can improve your leadership if — and it's a big IF — you understand and attend to these five fundamentals of becoming an exemplary leader:

1 BELIEVE IN YOURSELF.
Believing in oneself is the essential first step in developing leadership competencies. The best leaders are learners, and no one can achieve mastery until and unless they truly decide that inside them there is a person who can make a difference and learn to be a better leader than they are right now.

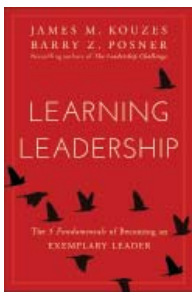
2 ASPIRE TO EXCEL.
To become exemplary leaders, people have to determine what they care most about and why they want to lead. Leaders with values-based motivations are the most likely to excel. They also must have a clear image of the kind of leader they want to be in the future — and the legacy they want to leave for others.

3 CHALLENGE YOURSELF.
Challenging oneself is critical to learning leadership. Leaders have to seek new experiences and test themselves. There will be inevitable setbacks and failures along the way that require curiosity, grit, courage, and resilience in order to persist in learning and becoming the best.

4 ENGAGE SUPPORT.
One can't lead alone, and one can't learn alone. It is essential to get support and coaching on the path to achieving excellence. Whether it's family, managers at work, or professional coaches, leaders need the advice, feedback, care, and support of others.

5 PRACTICE DELIBERATELY.
No one gets better at anything without continuous practice. Exemplary leaders spend more time practicing than ordinary leaders. Simply being in the role of a leader is insufficient. To achieve mastery, leaders must set improvement goals, participate in designed learning experiences, ask for feedback, and get coaching. They also put in the time every day and make learning leadership a daily habit.

Here's one habit you can start right now to apply these five fundamentals. At the end of every day, ask yourself this question: What have I done today to improve so that I am a better leader today than I was yesterday? Write down your answer. Do this every day, and in 10 years, that's 3,650 ways you've contributed to becoming your best self. L



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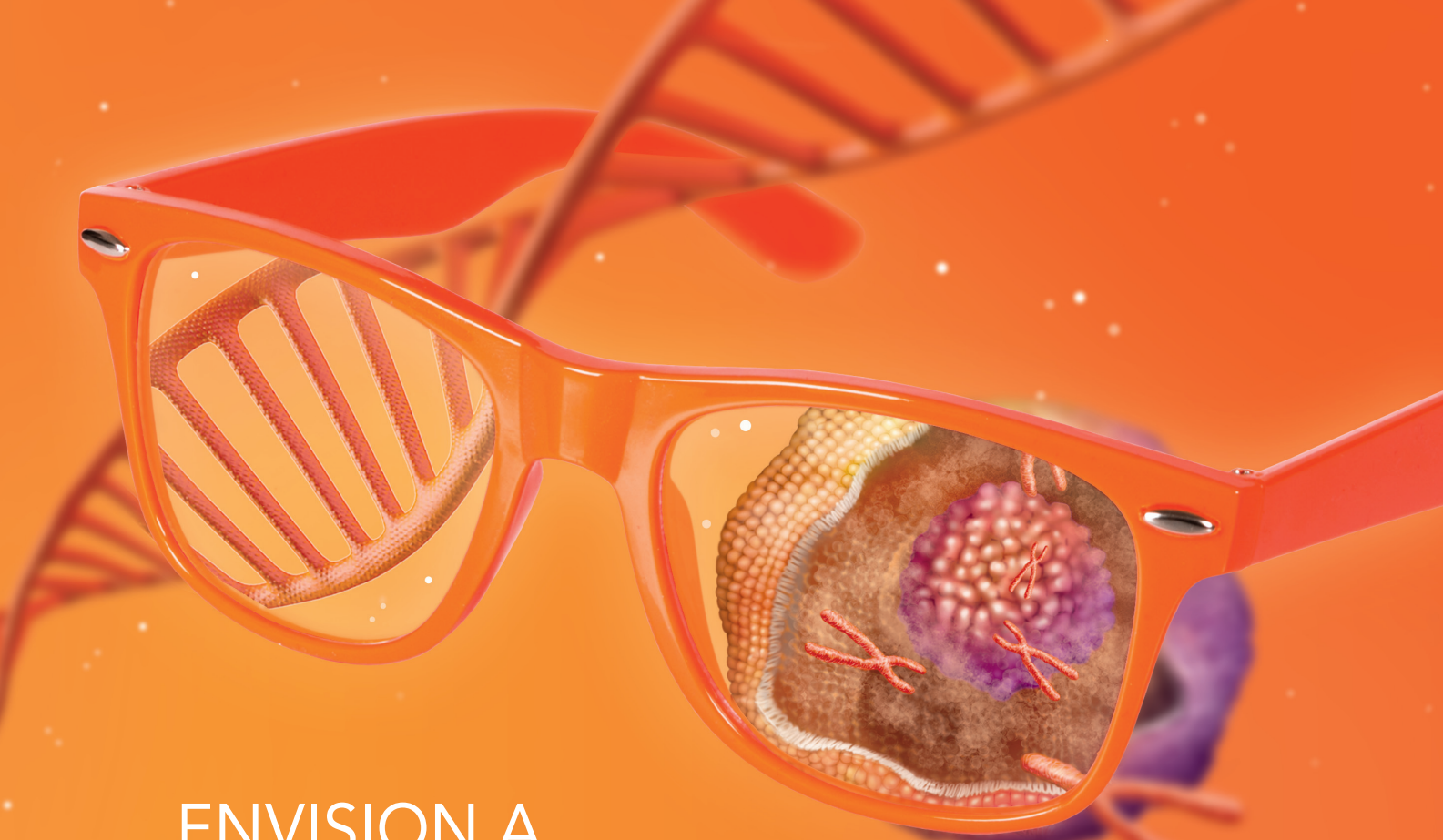

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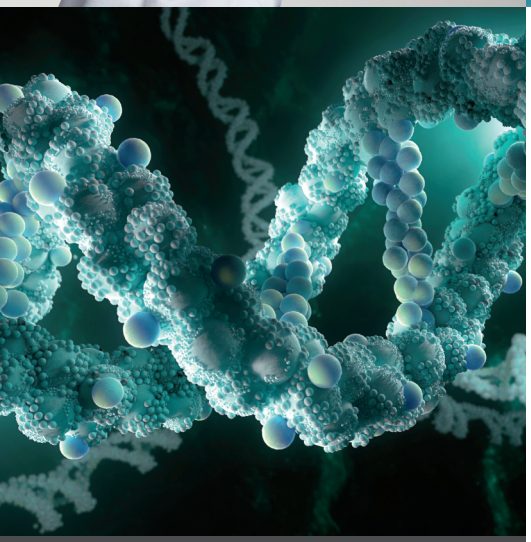

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