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JUNE 2017

How Pfizer & Zoetis Launched One Of The Most Successful Spinoffs – Ever

JUAN RAMÓN ALAIX
CEO, Zoetis

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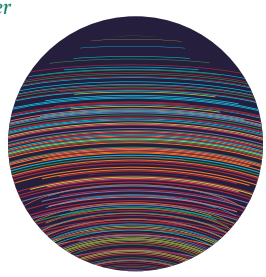

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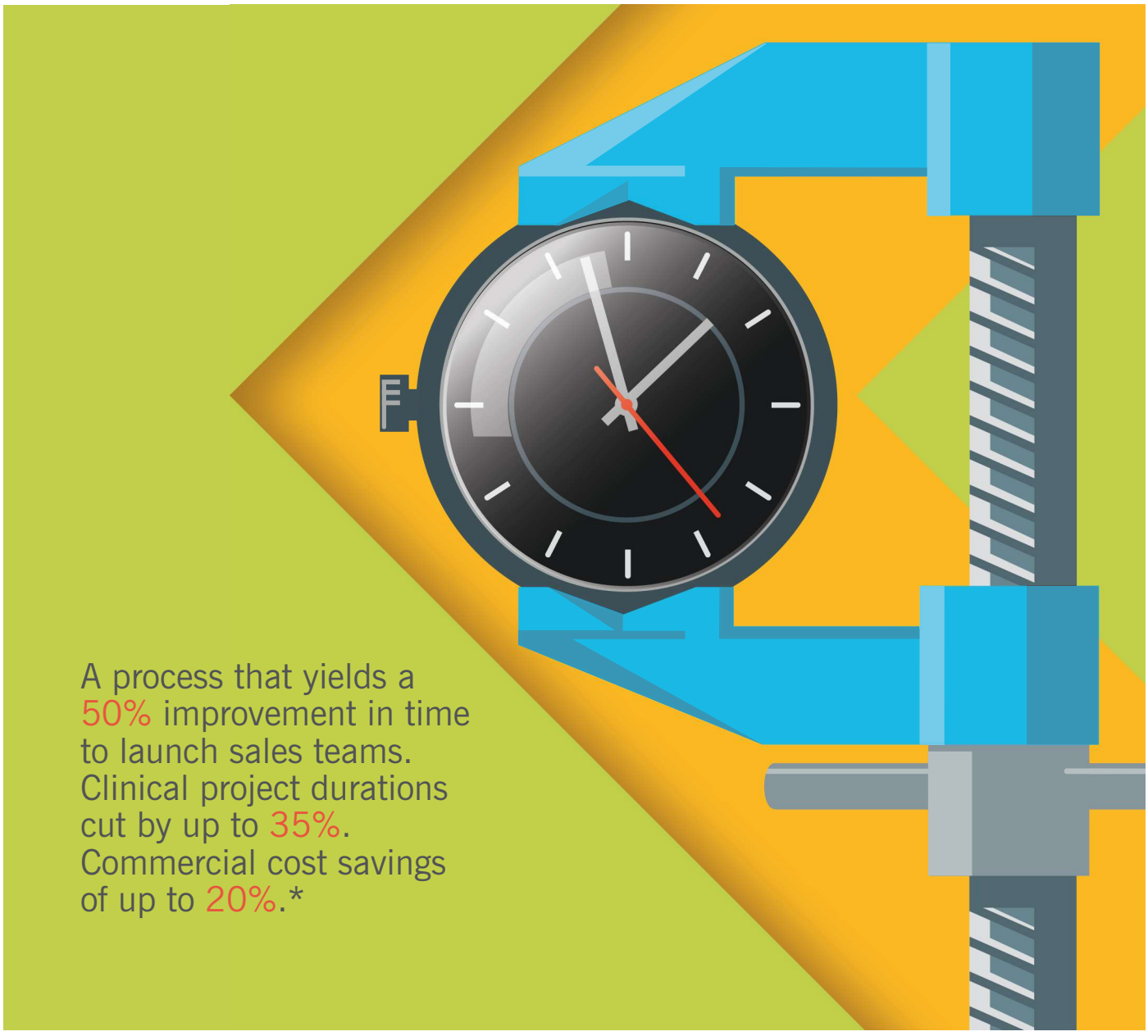

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Biopharma: Judged On Value By Those Who Bring Little

ROB WRIGHT Chief Editor

If you follow the U.S. stock markets, then you will probably agree that they tend to be a bit overreactionary. For example, in February, Under Armour, which had reported 26 straight quarters of 20 percent revenue growth, reported fourth quarter earnings of just 12 percent. As a result of the company's earnings falling by one penny per share, the stock's price plummeted by 26 percent. In April, it was announced that Express Scripts' biggest customer, Anthem, which accounts for $17 billion of the PBM's annual revenue, would not be renewing its contract. Despite the fact that the contract doesn't expire until the end of 2019, Express Scripts recorded an 11 percent decline in its stock price for the day.

If leaders of biopharmaceutical companies, who deal with drug development timelines of 12 to 15 years, responded in a similar "the sky is falling" fashion to a bit of bad news, do you think we'd ever see another innovative drug developed? Express Scripts has a year and a half to address the current situation. And as you will see by reading this month's cover feature on Zoetis, a lot can be accomplished in what the market might consider a rather short period of time. For example, in June 2012, Pfizer announced plans to spin off its animal health business. By the time Zoetis executed its IPO on January 31, 2013, Pfizer, considered by many to be a slow-moving behemoth, helped Zoetis train a CEO, build a governance board, establish a leadership team, secure a corporate headquarters, embark on the development of a corporate culture initiative … you get the point. Perhaps Express Scripts changes its business model, acquires a retail pharmacy chain, or merges with a health insurance company. There are a number of options on the table, and maybe the loss of Anthem, which is probably not a completely done deal yet, ends up being the best thing that ever happened to Express Scripts. My point is this — the markets (a.k.a., investors, analysts, etc.) could learn a lot from the patience and persistence the biopharmaceutical industry *has to* have.

Not long ago, I interviewed six former biopharmaceutical industry CEOs for an article in our upcoming July issue. One of the things that struck me was their response when asked, "As a CEO, what was your least favorite thing to do?" One executive answered, "Over the years I must have been at hundreds and hundreds of investor presentations, and I could have probably done with a couple hundred fewer." Another added, "Every buy-side investor believes they have unique insights into what your company could do to generate the best return for *them*." All agreed that having a good handle on investor relations is a critical aspect of being a CEO, and something that "comes with the territory." But for an industry measured on delivering more value to patients, the consensus among these industry icons was that the repetitive nature of investor's meetings delivered little. One former CEO put it best when he said, "When you are in an industry with very long time horizons, and people on a quarterly earnings call are worried about whether you've exceeded or fallen short of somebody else's quarterly forecast by a penny or two, that just struck me as not adding a whole lot of value."

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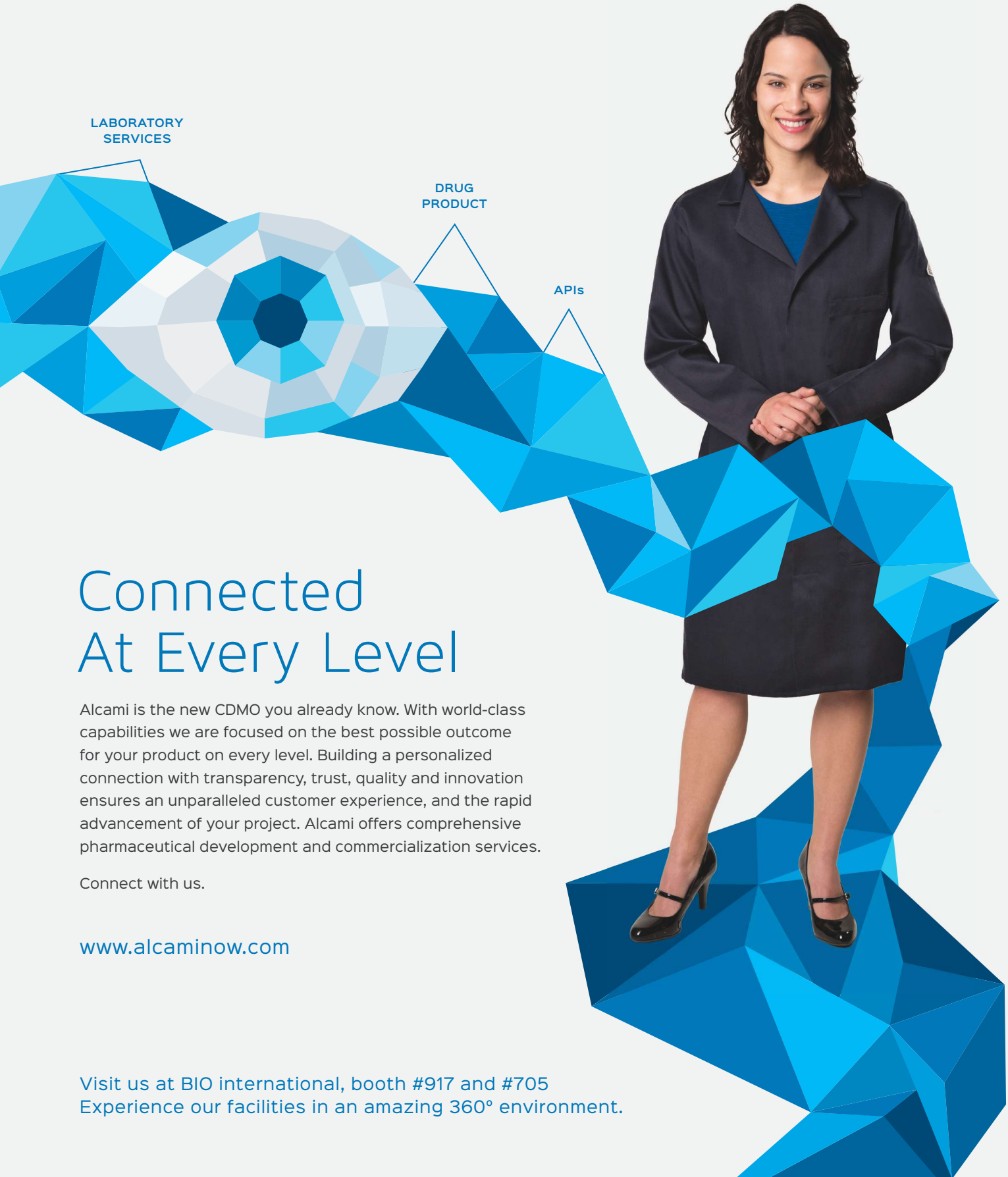

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Q What was your most difficult learning experience and how did you turn it into a success story?

A IN FEBRUARY 2010, President Obama charged me with dramatically increasing U.S. exports and to help create jobs. Despite 30 years in the private sector, making things happen would require governmental smarts. I assembled a team of globally savvy civil servants to complement my private sector skills. Together we transformed the culture and governance at the US & Foreign Commercial Service (USFCS), installed a structure mirroring the private sector, and inspired diplomats and bureaucrats to become "America's Sales Force." We rewrote strategy; redeployed 1,500 trade specialists across 109 U.S. and 129 global cities to "support business first," advocate for U.S. corporations in public procurement, serve as the export department for small and midsize enterprises; and enforced U.S. policy. By 2012 exports grew 16.4 percent to hit the high watermark of 14 percent of U.S. GDP, jobs created by facilitated exports more than doubled, and companies participating in trade missions grew by 233 percent.

SURESH KUMAR
was director general & assistant secretary of commerce in the Obama Administration and former EVP of external affairs at Sanofi, responsible for government affairs, market access, and corporate social responsibility.

Q What key trends are you seeing in clinical development?

A TWO TRENDS I AM SEEING include automation and disintermediation. That is not surprising, as these are two trends we have all been seeing in our everyday lives from autonomous vehicles to the business disruption created by the internet. Clinical trials lend themselves to opportunities to automate, given the emergence of platforms such as protocol templates (such as TransCelerate), data standards, eSource, and automated content generation. These areas, coupled with artificial intelligence and cognitive computing, create great opportunities to envision the "machine" that can serve clinical trials. Personally, I still like to see a steering wheel in a car, and I expect to still see the same level of human control and intervention in our clinical trials. When more of the process becomes automated, we will see quality improvements as well as disintermediation, and the question becomes: What steps, or even entire roles, will be impacted by such a future?

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

Q What advances are being made in gene editing, and what technologies will prove key in advancing this space?

A ZINC FINGER NUCLEASE (ZFN) TECHNOLOGIES are leading the field into in vivo human studies, and we expect other technologies will eventually catch up. Innovation in delivery technology will enable the genome editing field to advance into new tissue types such as the brain and will make dosing titration possible. Additionally, we believe in the near future there will be a new chapter in medicine with genome editing therapies providing permanent cures for many of today's most intractable and grievous illnesses.

SANDY MACRAE, M.B., CH.B., PH.D.
is president and CEO of Sangamo Therapeutics. He has over 20 years of leadership experience in the pharmaceutical industry encompassing various areas of clinical R&D and business development.

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Drug Costs Moderating, But Growing Copays Fuel Ire

JOHN MCMANUS The McManus Group

An irony in the simmering drug pricing debate in Washington is that net drug cost growth has moderated substantially, and of all the places to shoot, the industry still finds itself in the crosshairs of Democrats and Republicans alike.

At a Stanford University conference last week, Office of Management and Budget (OMB) Director Mick Mulvaney said President Trump keeps asking him what he is doing to address the high cost of pharmaceuticals. He then embraced a solution that had been pushed exclusively by Democrats: Medicaid-like rebates (aka price controls) in Medicare.

Mulvaney declared, "When Medicare Part D was put in, there was a tremendous giveaway to the pharmaceutical companies in terms of the fact that they no longer had to rebate like they did in Medicaid. So, we've actually floated that idea with the president to try and be a little heavier-handed on the rebates they have to pay to drive those prices down."

The Trump administration hasn't followed up on the remark, and considering Mulvaney (who, had he been a member in 2003, likely would have opposed MMA [Medicare Prescription Drug, Improvement and Modernization Act] as being an expansion to an entitlement) later strongly opposed price controls in Medicare, we must assume this is not a fully flushed-out policy priority. Yet it sent already-nervous pharmaceutical executives to DEFCON 2. The industry has been hearing that the administration is developing a list of policy options to address pharmaceutical pricing but never dreamed former Chairman Henry Waxman's (D-CA) preferred solution would be seriously contemplated by a top Republican cabinet appointee.

Moreover, the industry has become increasingly frustrated by the growing power of pharmaceutical benefit managers (PBMs) that demand and receive substantial rebates that cut into the margins of the pharma companies but do not seem to benefit patients. Indeed, privately negotiated rebates between brand manufacturers and PBMs have dwarfed sales growth:

- Credit Suisse analysis showed that gross sales had increased 90 percent from 2007 to 2015, but rebates had ballooned 262 percent in that period.
- QuintilesIMS Institute found that invoice prices had risen by double digits from 2012 to 2015 (topping out at 14.3 percent in 2014), but net price growth slowed to 2.8 percent in 2015.
- List prices increased 9.2 percent in 2016 yet net prices grew just 3.5 percent.

As a result, patients are paying artificially inflated prices at the pharmacy counter, which has fueled political resentment and demand for relief. Where is the spread going? Quintiles estimates that 28 percent of the total $450 billion pharmaceutical spend in 2016 goes to middlemen, often paid in retrospective rebates months after the patient receives and pays for a prescription at the pharmacy counter.

PBMs argue that retrospective rebates from pharmaceutical companies and fees collected from pharmacies are passed on to insurers, employers, and Medicare in lower premiums. This is the PBM's "trust us" argument that should fall flat with patients experiencing egregious out-of-pocket costs. This argument was substantially undermined last month when Express Scripts stock plummeted by 13 percent in a single day on news that its biggest customer, Anthem, announced it was unlikely to renew its contract. Anthem had sued Express Scripts for allegedly overcharging for prescription drugs to the tune of $15 billion. Anthem evidently is done "trusting."

Anthem's actions amplify what many policymakers are asking: Where are all these resources going? Rep. Doug Collins (R-GA), who has sponsored a bill requiring greater transparency of PBMs said, "What PBMs are experiencing right now is that both Wall Street and Washington are calling their bluff."

Pharmacies have ratcheted up their lobbying campaigns, rallying behind Collins' legislation and Rep. Morgan Griffith's (R-VA) bill to prohibit PBM's retroactive direct and indirect remuneration (DIR) fees. Although pharmacies lack the deep pockets of Big Pharma and the PBM industry, they have an incredible grassroots capability and enormous credibility of having the patient's best interests at heart with lawmakers.

They appear to be gaining traction with their arguments that DIR fees charged by PBMs are threatening their ability to provide high-touch services that improve patient adherence to their complex specialty medications.

IMPACT ON PATIENT FINANCIAL OBLIGATIONS

Patients are hit with a double whammy: copays on inflated prices of expensive drugs and increasing cost-shifting from health plans. A PwC study found that the percentage of plans requiring a deductible for pharmaceuticals had more than doubled between 2012 and 2016 — rising from 23 to 49 percent.

Likewise, cost-sharing has increased in Part D. According to an Avalere analysis, the average percentage of covered drugs facing coinsurance has increased over the past three years from 35 percent in 2014 to 58 percent in 2016. The percent of beneficiaries enrolled in Part D plans with more than one tier requiring coinsurance has skyrocketed to 96 percent in 2016 from 39 percent in 2014. Coinsurance on expensive specialty drugs is much more onerous for patients than flat copays.

Manufacturer copay assistance programs can help defray costs for patients in commercial plans, but the anti-kickback law prohibits the use of such programs for Medicare patients. Medicare patients must rely on charitable foundations. However, many foundations are under increasing scrutiny from the Office of Inspector General (OIG) and have caused some manufacturers to pull back critical support.

Yet while patient cost-sharing of expensive specialty medicines can be substantial, an often unnoticed truth is that the vast majority of prescriptions is for generic drugs. And those drugs have very modest or even no cost-sharing at all. Quintiles reports that 89.5 percent of prescriptions are for generics and 29 percent are dispensed with no copay at all.

Therein lies the genius of the American system. Under the Hatch-Waxman system Congress negotiated with the industry, brand-name companies can derive substantial returns on breakthrough products, but only for a limited time. Then generics can take over IP of the innovator product, enter the market, and drive prices down to the cost of production. The generic market is much more vibrant in the United States than Europe, and generics command a much bigger role in the U.S. According to the *2015 IMS Report,* Europe's generic utilization hovers around only 56 percent.

REIMPORTATION NOT THE SOLUTION

If Congress is unhappy with the returns generated by this system, then it should be addressed directly — monkeying in other areas without focusing on this fundamental deal isn't helpful.

One such persistent idea is importing drugs into the U.S. that are priced and initially sold in other countries. This past week a group of bipartisan senators led by Sen. McCain, Sen. Klobuchar, and Sen. Grassley urged the administration to use executive authority to lower prescription drug costs by certifying the importation of prescription drugs from Canada.

But as long as foreign price-controlled regimes artificially set drug prices abroad, there cannot be "free trade" with the U.S. Trump et al. are unhappy that other nations are not paying their "fair share" in terms of global costs of biomedical innovation. But allowing middlemen to leverage differential pricing systems is not the way to "get even." Oh, and we rather like our FDA-enforced gold standard drug distribution network. Four former FDA commissioners — Democrat and Republican alike — agreed in a letter to Congress that importing drugs from other countries is not the right approach. The commissioners warned of serious risks to consumers and patients because these drugs can be counterfeit, substandard, and unsafe. Nonetheless, legislation to reauthorize the Prescription Drug User Fee Act, now moving through congressional committees, will become a target for such populist hyperbole.

Congress' time would be better spent developing a Medicare Part D modernization package or working with the administration to address growing operational problems that Congress did not foresee when the benefit was first enacted in 2003. L

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The Case For A Healthcare Futures Market

DENNIS PURCELL Founder and Senior Advisor, Aisling Capital LLC

"If something cannot go on forever, it will stop."
— Herbert Stein

Herbert Stein, the noted economist, observed that when everyone believes that something won't change, it most certainly will. Throughout economic history, irrational excess in valuations and costs of assets has been a common occurrence. Recent expressions of this phenomenon include the soaring interest rates in the 1970s, the dot-com bubble of the 1990s, the housing bubble in the early 2000s, and the oil price shocks. During all of these bubbles, the prevailing sentiment was that price rises would go on forever in spite of collective intuition and plain common sense. And, as Dr. Stein observed, all these bubbles not only ended, but reversed — generally in spectacular and, not infrequently, disastrous fashion.

We are now living through a similar trend in the cost of healthcare, which has risen steadily and inexorably for the last 50 years and is now larger than the GDP of every country in the world except China and Japan. We spend more on Medicaid than defense in the U.S. According to the Congressional Budget Office, in less than a decade from now, Medicare, Medicaid, Social Security, and interest on the debt will represent $5.7 trillion out of a $6.3 trillion budget.

INSURANCE COMPANIES' CHALLENGES

The health insurance industry is faced with having to deal with an aging population that is certain to develop new health problems. At the same time, the pharmaceutical and biotech industries are developing effective but extremely expensive drugs to treat those conditions. Other factors such as nonadherence to drug regimens, spending on unnecessary treatments and procedures, and the advent of new but very expensive drugs that ultimately cure disease (for example, hepatitis C) are causing massive financial uncertainty in the insurance industry.

In other sectors of the economy, including agriculture, energy, and the financial industry (interest rates), there exists a robust futures trading market where industry participants can transfer risk and achieve predictable pricing while at the same time speculators can find opportunity in the trade. Risk transference and mitigation are essential to financial and operating cost management. These critically important financial tools, however, have been nonexistent in the healthcare sector.

Rather, in order to "bend the cost curve," the focus in healthcare is given to pricing and operational efficiency. Much commendable work is being done on how to attack the issue of pricing. Companies like Real Endpoints are comparing the relative value of drugs in the treatment of a particular disease. As the Affordable Care Act is likely to be amended if not replaced, we will continue to debate the relative value of drugs within the healthcare system.

Operational efficiency is also maturing. At HIMSS (Healthcare Information and Management Systems Society), 40,000 attendees browsed 2,000 exhibits, most of which were touting some way to improve operational efficiency. Improved electronic medical records (EMRs), interconnectedness among operating systems, and ways to enhance customer engagement were all on display. Many were truly impressive.

We believe, however, that in order to "bend the cost curve," financial management must be the underpinning going forward. Now is the time to develop a novel financial instrument which will provide risk transfer, transparency, and more certainty. A futures market in healthcare is a product whose time has come. Because of the advent of electronic medical records and Big Data, we now can collect detailed information by disease category.

FUTURES MARKET

A futures or forward contract is a legal agreement to buy or sell a particular commodity or financial instrument at a predetermined price at a specific time in the future. We will have contracts that are based on the cost of treating a disease (e.g., diabetes) just like energy (oil, gas) or agriculture (wheat, corn). The futures market has been important in other industries because companies can buy or sell futures to ensure future certainty. Jet Blue has the opportunity to lock in its cost of fuel. Ford Motor Company is pricing its new automobiles now and knows its cost of goods sold except the healthcare component, which is estimated at $2,000 per car. A review of large and midsize companies that are typically self-insuring themselves shows very comprehensive hedging strategies to deal with interest rate and currency risk. Yet, their healthcare risk is, by and large, not hedged at all. Even individuals who are facing higher deductibles and premiums don't have an effective way to manage the financial costs of their healthcare. In fact, 62 percent of all personal bankruptcies are due to medical expenses. The ability to mitigate this problem through new and better financial tools could provide real benefit to both consumers and producers of healthcare services.

> *"Now is the time to develop a novel financial instrument which will provide risk transfer, transparency, and more certainty."*

Until now, this has not been possible. In order for a futures market to exist, there must be a spot price (the current cost of the commodity). The units of product are self-evident in other markets (e.g., a barrel of oil or a bushel of wheat) but creating a meaningful unit for healthcare has before now been more challenging. Technology has recently provided an answer. Near universal adoption of EMRs enables both the ability to sort vast amounts of data into meaningful subdivisions, and to do it on a timely and reasonably frequent basis. Poliwogg has defined the healthcare "unit" as the cost of treating one patient for one disease for one year. This is the spot price from which futures contracts may be priced, as it is both consistent and scalable — an industry participant can now hedge its risk — whether long or short — in the financial markets, and do it at whatever level suits its particular situation.

Poliwogg is introducing the indexes that will underlie the financial management piece of the puzzle. The Poliwogg Therapeutic Indexes are a series of indexes designed to measure the direct and indirect costs of major chronic diseases in the U.S. They are suitable as the basis for a variety of financial instruments such as futures, swaps, options, or structured notes. The source data for the indexes is paid claims data derived from the largest database of claims currently available. The indexes will enable investors the first real opportunity to express an investment opinion on the course of a particular disease and its state of treatment.

The first index is the Poliwogg Diabetes Index, which includes all the costs (direct and comorbidities) of treating a Type 2 diabetic for one year. Simply put, the seller of the diabetes future (most likely a natural participant) will lock in the price of treating diabetes, and the buyer of the diabetes future (most likely a financial institution) will see that fixed amount back to the buyer. The risk and return of diabetes costs (as measured by a well-constructed index), either being higher or lower than the index, will be borne by the buyer of the index. Going forward, as the futures concept matures, we will be able to provide sub-indexes with more precise measurement and management.

This is an ambitious undertaking. The cost of treating diabetes in the U.S. is already higher than the cost of the oil we use. At over $300 billion annually, every transaction that goes into treating a diabetic is economic in nature. The list of participants in the market is very long, and includes insurance companies, self-insured corporations, pension funds, hospital systems, physicians groups, device manufacturers, medical service providers, drug and biotech companies, and financial institutions. Each one is striving for stability in the market so they can adequately plan for their business going forward. L

DENNIS PURCELL, a founder and senior advisor of Aisling Capital LLC, has completed over 200 transactions and supervised over $15 billion in life sciences industry financing and advisory assignments.

Frequency Therapeutics

A small molecule approach to regeneration of hearing cells and other damaged tissue

WAYNE KOBERSTEIN Executive Editor
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SNAPSHOT

Frequency Therapeutics is an early-stage developer of small molecule drugs to activate "progenitor cells" and restore healthy tissue. Its lead program is in treating hearing loss by regenerating sensory cells in the inner ear, for which it is planning a Phase 1 trial to launch in mid-2018.

WHAT'S AT STAKE

Frequency is yet another industry reverberation from the inventive activities of Dr. Robert Langer and his lab at MIT. My conversation with the company's cofounders, David Lucchino, president and CEO, and Chris Loose, Ph.D., chief scientific officer, starts out in 2006, after Loose, top of his class at Princeton, joined the Ph.D. program at Langer's lab and teamed up with Lucchino to win the lab's business competition. Their business plan? Start a company, Semprus BioSciences, that would develop and gain FDA clearance for a new biomedical technology by 2012. They met their goals, winning the clearance and selling Semprus, then counseled with Langer about what to do next.

"Dr. Langer was very passionate about finding a way to get the disease-modifying benefits of gene therapy or CRISPR — but without drug delivery complexities or permanently changing the genetics of the body," says Loose. "He asked, what if we could just leverage the stem or progenitor cells that are already in your body, and just give them a simple cue with small molecule drugs that activate them in place to restore healthy tissue and function? That led to what we now call Progenitor Cell Activation or PCA technology. He was passionate about PCA being a whole new mode of medical therapy."

Lucchino and Loose sensed the business potential of Langer's concept once the team found ways to control cells called Lgr5 progenitors, present in the ear, with small molecule drugs to restore the hearing cells. "It is when we are in our mother's womb that the hearing function fully develops, and it is turned on even before you were born. So the hearing cells you're born with are the same ones you die with," Lucchino says. "Dr. Langer and the Frequency team figured out how to take advantage of this biological anomaly and hotwire it temporarily using small molecules to get it to regenerate itself."

Two factors ensure the action is temporary and precise: The drugs only need to be present a short period of time, and the activated cells are contained only in their proper place in the ear, the cochlea, after local infusion. "We actually will do a simple injection across the eardrum, which is a procedure done all the time for steroids or antibiotics, and then the small molecules can easily diffuse where they get together to get to the progenitors to reawaken cochlear cells," says Lucchino.

With hearing loss now almost as common as farsightedness, hearing aids remain the sole solution available and have become considerably cheaper, but simply amplifying sounds in the ear cannot solve the biological problem and may only add to the harm over time. One advantage of having a large potential market will hopefully be an almost limitless patient pool for clinical trials. Another, if investors continue to find the company's concept plausible, will be in funding the actual trials.

But the ultimate advantage of success would be the practical logic behind the company's primary approach. "In the history of regenerative medicine, many have taken a really challenging approach: removing cells from the body, manipulating them, and then trying to put them back into the right spots, to do the right job," Lucchino says. "That was one of Langer's insights — just use the progenitor cells that are already in place and programmed to do the right job — and that is the heart of our technology." L

DAVID LUCCHINO
Cofounder, President, CEO

Vital Statistics

16
Employees

Headquarters
Woburn, MA

Finances

2017 Series A Funding Round
$32M

Lead Investor
CoBro Ventures

Latest Updates

April 2017:
Announced $32 million Series A financing to support clinical development of a first-in-class hearing restoration therapeutic.

February 2017:
Announced novel small molecule approach to restore hearing, published in *Cell Reports*.

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HOW PFIZER & ZOETIS LAUNCHED ONE OF THE MOST SUCCESSFUL SPINOFFS — EVER

ROB WRIGHT Chief Editor @RfwrightLSL

JUAN RAMÓN ALAIX
CEO, Zoetis

Spinning off a $4 billion biopharma business is no easy task. Integrated functions need to be separated, governance boards created, leadership teams assembled, and corporate headquarters established. And those are just *a few* of the tasks Pfizer faced when announcing the decision to spin off its animal health business back in 2012. A CEO also needed to be chosen for this soon-to-be, completely independent animal health company.

ENTER JUAN RAMÓN ALAIX.

Since 2006 Alaix had been responsible for managing the Pfizer animal health business, a fact that made him the likely candidate for the new job, except for one thing — he had *never* been a CEO. That one missing ingredient has been known to turn what seems like a logical decision into a colossal catastrophe at some companies. Pfizer wasn't about to take that risk. What follows is the story of how Alaix was groomed for his new role and how Zoetis turned into the world's *largest* publicly traded animal health company with a per-share stock price outperforming that of its former parent.

STEP 1: PREPARE THE LEADER

"Now is the time to prepare yourself." That's what Pfizer CEO Ian Read told Alaix after the company's board had recommended Alaix to be the CEO of Zoetis. "He wanted to make sure I continued growing the business while it was still part of Pfizer while also preparing for the separation and preparing *myself* for the new role," Alaix recalls. Being the CEO of a public company is very different from running a division within a parent organization. Within a business unit there are some areas where you have complete control (e.g., commercial, R&D) and others where you have responsibility but rely on the parent company for support (e.g., financial reporting). While the head of a business unit might periodically provide an internal financial update, a CEO provides routine financial updates to internal and external stakeholders and often in very public forums. To help prepare Alaix to be Zoetis' CEO, he undertook an aggressive 18-month training program.

The first part of his training was to work with Pfizer HR to define a personal development plan, through which it was determined he would benefit from being mentored by an experienced CEO from outside the company. Pfizer employed the services of Merryck & Co (an organization that specializes in leadership development), which put Alaix through a series of assessments to identify skill gaps. Merryck also provided him with a list of proposed mentors, from which Alaix chose the former CEO of a big European company. Meetings with his mentor began with a two-day retreat, after which they would usually speak on a monthly basis. Alaix found value in being able to bounce ideas off an outsider who could listen to his concerns and challenge him to think differently.

Another component of his CEO training involved a communications expert. Alaix had little experience with some of the communications required of a CEO (i.e., being comfortable doing print and TV interviews). "Before the IPO I was responsible for doing two road shows," he shares. This was the first time he had such a responsibility, and his delivery of the Zoetis strategy to analysts, investor groups, and media would play an influential role in determining the company's value. During his communication training he employed two different trainers to improve his skills in a variety of communication venues (e.g., small group presentations, keynote addresses, quarterly earnings calls). "But I had other help too, such as bankers and a lot of internal people who assisted in framing up the Zoetis strategy in a way easy for investors to understand," he concedes.

ZOETIS EXPERIENCES EARLY GROWING PAINS

On May 16, 2013, Zoetis, which only three months earlier had been spun off from Pfizer as a completely independent company, got some very welcome news — an FDA approval for APOQUEL (oclacitinib tablet), which helps control severe itching associated with allergic dermatitis in dogs 12 months of age or older. But the drug launch did not go as smoothly as planned. "We made some conclusions based on market research that turned out to be false," admits Zoetis CEO Juan Ramón Alaix. For example, market research indicated that the drug's efficacy would be comparable to some existing therapies. In addition, veterinarians felt that the side effects of many of the existing therapies weren't that severe, and something they could easily manage. "We had built our inventory based on this information," Alaix shares. It wasn't very far into the launch that Zoetis ran into a problem of being able to adequately supply the market. "Soon after launch we were getting market feedback that efficacy was much better than existing therapies," he states. "And with regard to side effects of existing therapies being easily managed by vets, pet owners were the ones often having to deal with these, which they found to be problematic." As a result, demand significantly exceeded Zoetis' expectations.

The company worked toward ramping up supply, but manufacturing APOQUEL is fairly time consuming. "It takes about a year, not just a couple of months," Alaix attests. "It starts with the ordering of registered materials, which can take several months when you factor in shipping, clearing customs, etc. Then the production of the API, which is another seven to eight months, before we move on to finished

goods." As a result, for many months Zoetis had some very frustrated customers wanting to use APOQUEL. High demand and lack of product supply created a significant negative market reaction. "It is very disappointing for any organization to have such a good product and not be able to meet customers' expectations."

One of the goals when first formulating the Zoetis spinoff was to create a corporate culture that lacked silos. The pain experienced from this failure to supply customers reinforced this desire when it came to preventing this as a future problem. "Improving market research was certainly an opportunity," Alaix stresses. "But there were other learnings from APOQUEL." For example, Zoetis learned that the commercial organization didn't fully understand the complexity of APOQUEL manufacturing. "When we are developing a process, it needs to work in a very integrated fashion," Alaix explains. "All functions need to be well aligned before launch [i.e., R&D, commercial and manufacturing]." Today, when Zoetis has a product in development, rather than involve commercial or manufacturing during later stages, the company includes these disciplines much earlier, so everyone understands the product's needs and volumes. "To reduce risk and have better coordination means all functions have to have full information about all the different activities and decisions being made."

The company now also develops best- and worst-case scenarios, so they can have plans in place to react quickly and appropriately. One such plan was used when launching CYTOPOINT, a sterile liquid containing a monoclonal antibody (mAb) for treating dogs with atopic dermatitis. "We built the capabilities to produce our own mAbs," Alaix shares. "I believe this has put us in a situation where we will be able to meet all of our customers' needs, even if demand exceeds our initial projections."

STEP 2: PREPARE THE MARKET

For Alaix, the key to communication (and preparing the market) has been overpreparation. When it was time to actually execute his first real Zoetis road-show presentation, he had already done it dozens of times. "One of the road shows was geared toward the company IPO," he states. "On February 1, 2013, Zoetis went public and we raised $2.2 billion." This was when Pfizer sold approximately 20 percent of its stake in Zoetis. Three months later, Pfizer announced plans to spin off its remaining 80 percent company stake. "Preparing the market for Pfizer's divestiture of its majority stake was what I discussed in the other road show."

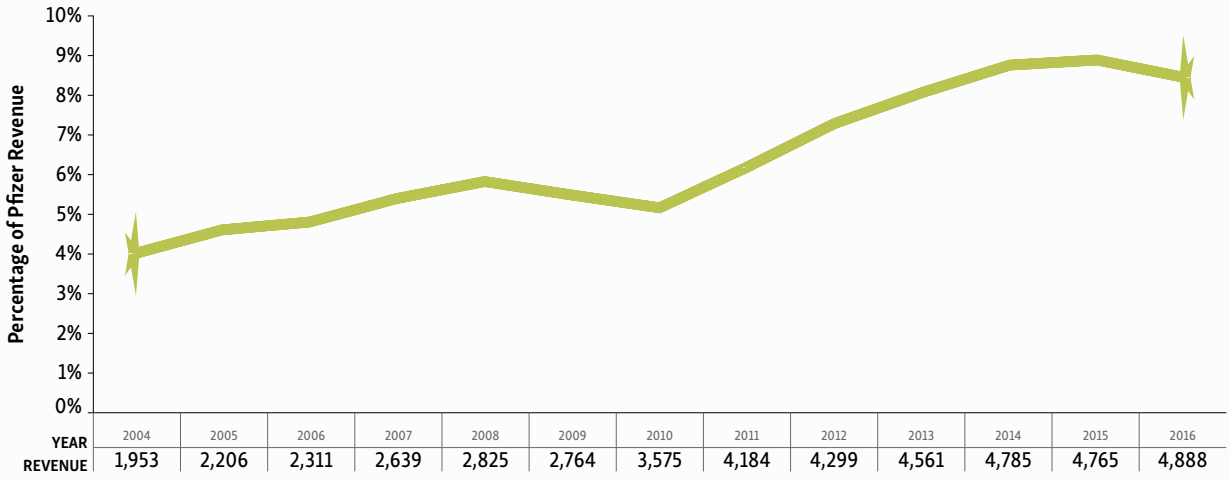
For each of these two presentations, Alaix had to deliver two types of information. First, he had to explain the difference between the human health and animal health industries. Second, he had to help investors understand why Zoetis was well prepared to be a completely independent animal health company. "Many of the people that were listening to us were analysts and investors very familiar with human health but had little knowledge about animal health," he says. For example, many were surprised when Alaix described the animal health business as having nearly zero involvement by third-party insurance payers. "Our customers are veterinarians and livestock farmers, and when they make the decision to buy, they are also paying for their purchases."

Another difference between animal health and human health is generic incursion. "In human health when you lose patent exclusivity, your revenue erodes by 90 percent within the first year," he explains. "In animal health when a drug loses exclusivity, it might take five years to have an erosion of between 20 to 40 percent." In fact, of Zoetis' top 24 portfolio products, the average amount of time on the market is roughly 30 years. "Many are still growing in sales," Alaix asserts. Animal health companies are less dependent upon the introduction of new products to compensate for generic incursion. Other differences include lower drug prices, as well as lower profits. "The average net gross profit in animal health is about 60 to 65 percent, which is a lot less than human health." Generic companies are more interested in competing in the human health space because there is a significant opportunity to compete on price and still be profitable. "There is less pressure to lower animal health drug prices as there is less opportunity to do so."

Another difference between the two industries is required infrastructure. "To reach customers [i.e., veterinarians] in animal health requires much more infrastructure," Alaix contends. To effectively market and sell animal health products requires an extensive field sales force, which not only decreases animal health profitability, but also inhibits generic competitive entry. Consider this: About 14 percent of Pfizer's 96,500 employees are members of its global field force, while approximately 29 percent (i.e., 2,610) of Zoetis' 9,000 employees make up its global field sales force.

Another difference Alaix had to explain during his road shows was how animal health companies invest in R&D. "In our case, we balance our investing in new products while continuing to invest in our current portfolio of 300 product lines with new formulations, indications, combinations, and/or geographic expansions," he explains. "Expanding the life cycle of our portfolio is a different R&D model that has the benefit of being much more predictable and less impacted by price." This predictability is a hallmark of animal health. "For the last five years the animal health industry has had steady growth of between 5 to 6 percent, and is projected to grow at the same rate in the future," he adds. In addition to being predictable, animal health is also resilient. "Even during the economic crisis of 2008 and 2009 [excluding the impact of currency exchange], the industry grew," Alaix shares. "A highly stable and predictable industry is very attractive to certain investors."

ZOETIS WORLDWIDE ANIMAL HEALTH REVENUES



YEAR	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
REVENUE	1,953	2,206	2,311	2,639	2,825	2,764	3,575	4,184	4,299	4,561	4,785	4,765	4,888

Revenue in millions
NOTE: 2013-2016 Represents estimation of Zoetis percent of Pfizer revenues had it not been spun off.
NOTE: Revenue figures from 2004-2012 were taken from Pfizer's annual reports, while 2013-2016 were taken from Zoetis annual reports.

STEP 3: PREPARE THE COMPANY

When it came time to choose a name for the new company, they started with 1,000 options, winnowed the list to a top 10, and ultimately chose Zoetis, which is derived from the word zoetic, meaning "of or relating to life." "We also liked the idea of the name beginning with a 'Z' and an 'O,' making it close to zoo, a word highly associated with animals," Alaix says.

As part of the IPO preparation, Alaix also wanted to define the new company's mission, vision, and culture. "We wanted to make sure these were not an extension of what we had been within Pfizer, but something closer to where we wanted to go as an independent company."

THE ZOETIS VISION

- Our products, services, and people will be the most valued by animal health customers around the world.

THE ZOETIS MISSION

- We build on a six-decade history and singular focus on animal health to bring customers quality products, services, and a commitment to their businesses.

"Being a small company with a single focus on animal health, we saw the opportunity to create a culture with a strong sense of ownership," he points out. As part of Pfizer it was very difficult for the animal health organization to "move the Pfizer needle" in terms of value (i.e., increasing earnings per share). "We only represented 5 to 7 percent of Pfizer's total revenue. But as a much smaller independent company, a $5 million change after tax adds one penny in earnings per share at Zoetis." Because Zoetis employees can see how what they do every day impacts the company's value, Alaix believes they have a stronger sense of ownership than when they were part of Pfizer.

The company also wanted to eliminate silos, a message reinforced by an early lesson learned by Zoetis (see sidebar "Zoetis Experiences Early Growing Pains"). "When you are part of a big corporation as a business unit, some of the functions are within the business unit and others are outside of the business unit. As Zoetis, we had the opportunity for every colleague to have the same objective and focus, while eliminating that sense of territorialism."

Preparing Zoetis to be a separate company also involved developing a corporate governance board and an executive leadership team. Alaix says he wasn't concerned if these leaders had previous animal health experience. "I sought experience in various corporate functions that an organization operating as a business unit would typically lack." Having been at Pfizer since 2003 provided Alaix the opportunity to identify and develop top talent existing throughout the Pfizer organization. But he had some other help. Prior to the IPO, Pfizer created an internal board to oversee the building of Zoetis, and Alaix met with this group monthly. The internal board included Pfizer's CEO, Ian

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Read; Pfizer's CFO, Frank D'Amelio; and several other top company executives.

While still part of Pfizer, the animal health division was tasked with conducting business as usual while also preparing for the future. As such, Alaix didn't want to involve commercial or R&D in any part of the reorganization. "I wanted these two teams to remain intact and focused on what they were doing." Other areas such as business development, finance, HR, IT, and manufacturing were tasked with defining what their future operating models should be as well as what tools they would need to operate independently from Pfizer. For example, a new enterprise resource planning (ERP) system from SAP was chosen with a plan of having it fully operational within 18 months of IPO. That's an aggressive timeline, but Alaix knew that to have a successful separation, Zoetis needed to have full control of its operations.

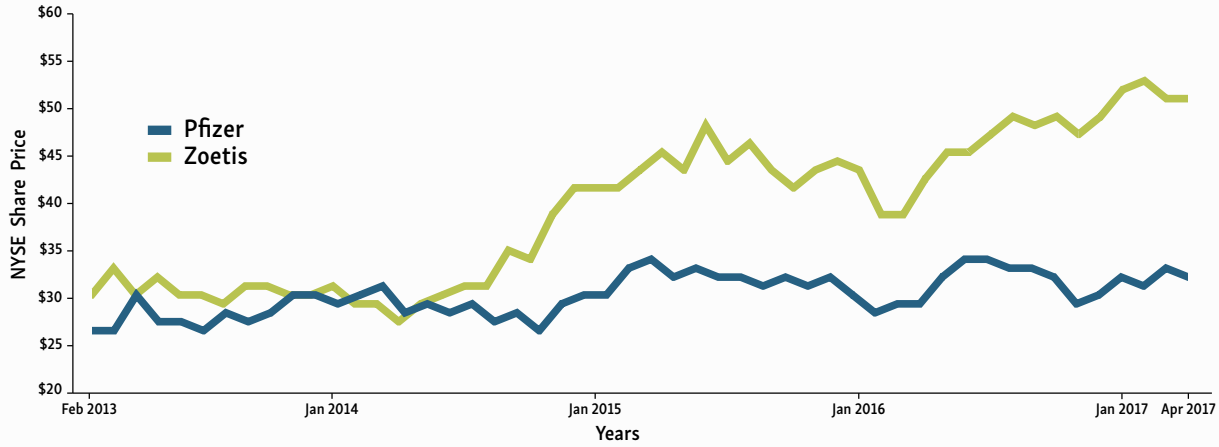
The company also needed to figure out things such as appropriate department cost structures, best practices, and appropriate global geographic reach for a company of its size. For instance, as part of Pfizer, the unit operated in about 70 markets. "But we determined that as an independent company, continuing to operate in all of these countries in the same manner added complexity and cost without providing the right level of return," Alaix explains. As part of an operational efficiency initiative begun in 2015, Zoetis moved 25 of these geographic locales from a direct-service model to a distribution-service approach. As the remaining 45 markets drove 95 percent of the company's revenue, the move had minimal impact on Zoetis revenue.

During the efficiency initiative the company also sought to reduce its number of product offerings. "At Pfizer we were operating with 15,000 SKUs," Alaix shares. "To be more efficient from both a financial and manufacturing perspective, we decided to eliminate about 5,000 SKUs." This allowed Zoetis to have a better commercial focus on the products that really mattered, not only for its customers, but for the company itself.

Another primary objective was making sure that Zoetis operated as financially efficient as possible. Determining this took some time, and here's why. Despite having a finance team in place, Zoetis was still initially dependent on Pfizer for its financial reports. "We knew the process of fully separating from Pfizer for some functions such as finance would take some time," Alaix states. "But as we identified these opportunities early, we were able to fully implement our own finance system by the first quarter of 2016." Alaix notes that other areas, such as HR, communication, and business development, moved toward independence almost from day one.

Despite some minor growing pains, the spinoff of Zoetis from Pfizer has been a remarkable success. In fact, there are probably a few Pfizer investors currently kicking themselves for not jumping at the chance to become Zoetis shareholders. For when Pfizer decided to sell its majority stake in Zoetis three months after the IPO, Pfizer shareholders were offered the opportunity to exchange $100 worth of company stock for $107.52 worth of Zoetis stock — a 7 percent discount. And while both companies continue to be highly successful, a side-by-side comparison shows that since Zoetis went public, the company's share price has increased by more than 74 percent. During that same time period Pfizer's share price has increased by a respectable 22 percent. That's not a bad performance metric for a company with a first-time CEO.

SHARE PRICES FOR PFE AND ZTS FROM DATE OF IPO TO PRESENT



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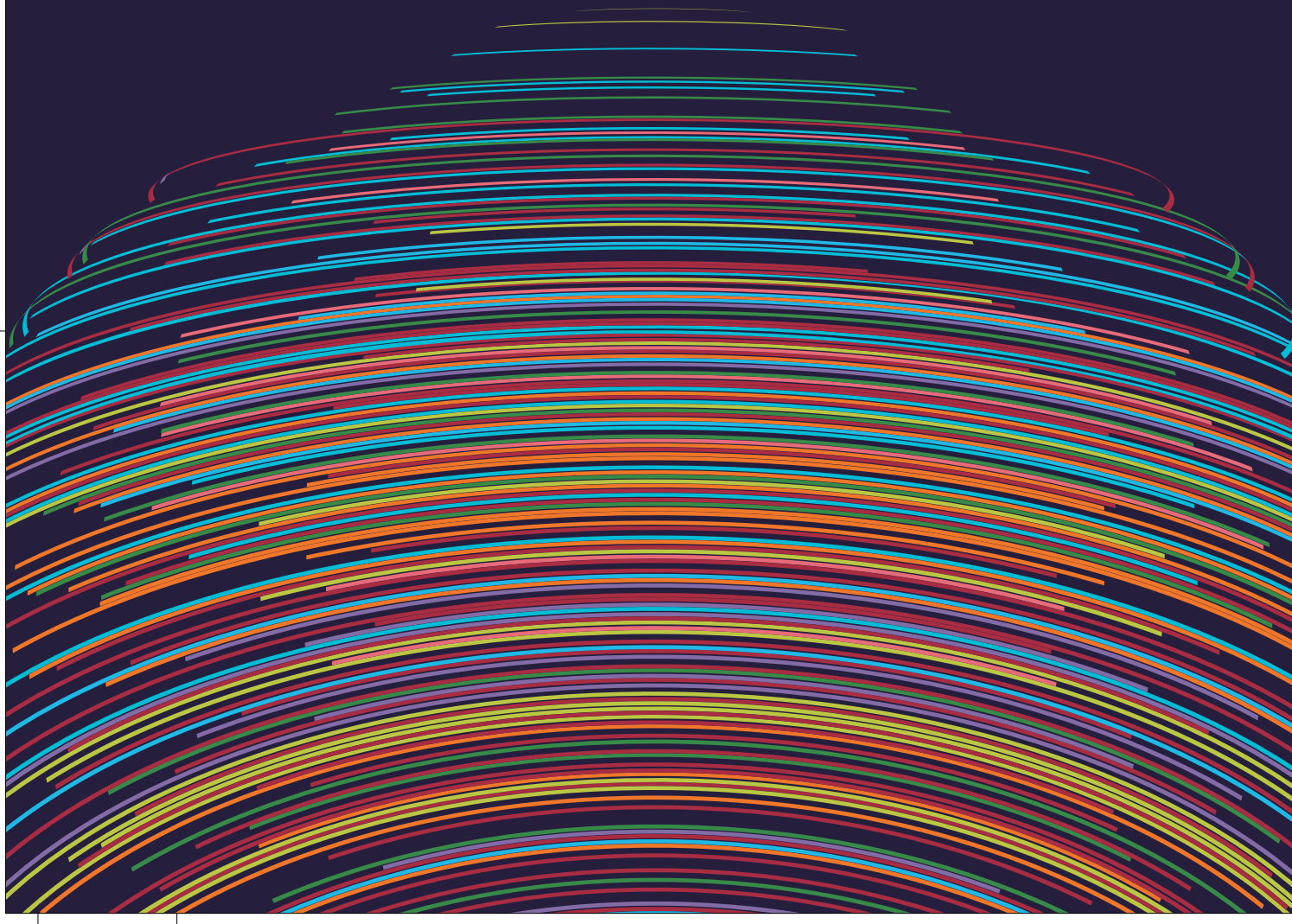
IMMUNO-ONCOLOGY TAKES OVER

OUR ANNUAL CANCER IMMUNOTHERAPY UPDATE: 2017

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein



When we started our series, "Combination Cancer Immunotherapy — A Virtual Roundtable," in 2014, our basic assumptions were not the consensus view. We assumed immunotherapy, now more commonly called immuno-oncology (IO), would become the dominant form of cancer treatment and central target of academic and industry research in oncology. We assumed a single, backbone therapy would become the pillar around which combinations of therapeutics with complementary targets would form. And we assumed the IO field, especially in its combination approaches, would pose profound scientific and business challenges as it took over as the central focus of oncology in general. Our assumptions turned out to be correct. Now, all IO has to do is catch up with itself.

This annual update of our original series takes a look at recent research and commercial efforts to deal with the ramifications of the IO revolution. We have published two other IO Updates, in 2015 and 2016. This year, we spoke with some of the key opinion leaders who participated in the previous discussions, caught many of the key findings presented at the annual AACR conference in April, and looked at the topics likely to arise at the annual ASCO conference in June. Two major themes at both events will surely echo our first assumptions: First, immuno-oncology has climbed to the top of oncology more quickly than even its initial supporters imagined. Second, IO combinations will win adoption in practice based on continuing research into immune mechanisms alongside a massive effort in clinical development.

That research has gained momentum for more than "academic" reasons. The new immunotherapeutics, especially the PD-1 inhibitors such as Opdivo (nivolumab) and Keytruda (pembrolizumab), have shown they can produce lasting benefits for patients beyond anything seen before, but of course not for all patients all the time. As evident at AACR — and predictably so at ASCO and other related meetings — the IO community's attention has largely shifted to the question of why cancers in some people respond to immunotherapy, why others do not respond or relapse later, and what can be done to turn non- or poor responders into good responders. Mechanistic understanding may be the main avenue toward new agents that outperform or boost the performance of the current ones. At the same time, however, leading researchers and companies have taken the empirical route with hundreds of clinical trials probing new possibilities.

One answer to the responder/nonresponder issue is that the picture seems to improve as new trial data comes out and approvals for new drugs and indications mount up. One of our regular KOL contributors, Jedd Wolchok, M.D., Ph.D., of Memorial Sloan Kettering Cancer Center (MSK), sees the promising data arising from continuing development of the first two approved drugs in the class. Wolchok and his team have been conducting some of the seminal trials with checkpoint inhibitors, as well as other immune-modifying agents as potential complements.

"The combination of CTLA-4 and PD-1 blockade in melanoma with ipilimumab and nivolumab was approved late in 2015, but we got the first glimpse at the survival data from the Phase 3 study at AACR this year, with the very fortunate outcome that the number of patients who died on the study was well below projections based upon prior data. Thus, there is still no median OS reached for the PD-1 blockade or the combination blockade group," Wolchok says. "Of course, it is good to see how much progress has been made in melanoma, but it is great to see the same combination in later-stage trials across different disease types using doses and schedules that have been adapted to maximize safety in each type. We have a lot of work going on to optimize the use of the combination strategy in a large variety of solid tumors and hematologic malignancies."

Susan Slovin, M.D., Ph.D., of MSK, agrees that immuno-oncology has progressed and, like most research leaders in this field, has an individual take on where it is headed: "There has been greater emphasis made on trying to understand the tumor microenvironment and how the checkpoint inhibitors may influence specific immune populations. The new idea of tissue residual memory cells to provide immune surveillance is a novel concept under evaluation. Another important milestone is the impact of CAR [chimeric antigen receptor] T cells on the hematologic malignancies and several new approaches for their use in solid tumors."

Alan Venook, M.D., of UCSF, who voiced the most skepticism about the new immunotherapies in our original virtual roundtable, has moderated his views since then, based on subsequent clinical data. "The biggest change has been the expansion of the population of patients and diseases who benefit from checkpoint inhibition," he says. "Less dramatic, but still important, has been the evidence that combination inhibitors, such as CTLA-4

plus PD-1, are even more impactful. Obviously, these developments change the flavor of current and future research plans. I remain pessimistic of how broadly these will work and what long-term consequences might be, but both the breadth of activity across a number of diseases and, more importantly, the extraordinary responses we see in some otherwise refractory patients, make it clear that checkpoint inhibition has ushered in an entirely new era of immunotherapy."

"Unfortunately, despite promising preclinical data, many novel immune therapies do not prove perfect within clinical trials," says Slovin. "So we may be revolutionary in the moment for some diseases, but we still haven't figured out why some cancers have minimal responses to the current armamentarium. That, to me, remains the most interesting question."

QUICK STUDY

Day by day, our bodies fight cancer. Tiny spots of precancerous or cancerous cells rise up, only to die under the close scrutiny and powerful assault of the immune system. Occasionally, and in some individuals, part of the cancer survives and evolves by randomly adaptive mutation to protect itself from killer T cells and other immune cells that would ordinarily recognize and destroy it. The growing tumor avoids immune detection and response not by hiding behind a mask, but by performing a sort of cellular hypnosis, effectively turning the attacking cells off or even enlisting them as cancer co-conspirators.

Also called leukocytes or lymphocytes, T cells are classified by the CD (cluster of differentiation) number, such as CD8+, each one coded to a certain set of antigens the CD cell type expresses on its surface. T cells change identity and function by expressing different antigens. The same T cell can be a memory, killer, regulatory, or any other type, depending on the antigens it expresses. "Successful" tumors check an immune attack by evolving and adapting the ability to manipulate T cell identity, inactivating or turning memory (CD4+, CD8+, or TM) and killer (CD8+ or TK) T cells into regulatory (CD4+, CD25+, or Tregs) T cells that suppress immune response. Note: T cells that perform widely different functions can share the same CD codes; the antigenic variations between TM, TK, Tregs, and their various subsets, for example, are subtle and still far from completely understood — and therein lies one potential vein for extracting knowledge about the variable effectiveness of IO agents.

Checkpoints are essentially antigens that tumors induce T cells to express, typically turning the T cells into Tregs that shield the cancer from immune response. But the most significant defensive tool the tumor wields, PD-1 (programmed cell death protein 1), acts only partly as a checkpoint inhibitor, inactivating the CD8+ cells by binding them to the PD-L1 ligand on the tumor cell. PD-1 inhibitors also appear to up-regulate a host of TNF (tumor necrosis factor) receptors that stimulate populations of activated killer T cells to expand and attack the tumor.

So far, the clinical data supports the strategy of blocking PD-1 as superior to blocking its ligand, PD-L1. Also, research studies suggest the more a patient's tumor expresses PD-1/PD-L1, the more likely the patient will respond positively to anti-PD-1 or anti-PD-L1 therapy. Still, the jury is out and having a big argument over that supposition, based on the questionable accuracy of biopsies assessing PD-L1 status in tumors, which are notoriously heterogeneous.

Yet the clinical results outweigh all kibitzing; anti-PD-1 works much, much better than older approaches — for so many more patients, with much more lasting benefit, and incomparable safety. Anti-PD-1 also significantly outperforms its closest IO competitor, anti-CTLA-4 (Yervoy/ipilimumab). Although less than 50 percent of treated patients may have a significant benefit, the positive results of anti-PD-1 are often dramatic and some believe they deserve the label "cure."

Although the resounding theme at AACR projected a consensus about the anti-PD-1 predominance and we heard no one challenge its position directly, many presenters and some of the key opinion leaders we interviewed spoke of checkpoint inhibitors more equivalently. They usually mentioned anti-CTLA-4 in the same breath and are perhaps still looking for a new challenger to emerge from among the many other checkpoint candidates. Nevertheless, for the time being, the predominance of anti-PD-1 therapy in IO seems beyond question.

BIG KID ON THE BLOCK

Two large pharma companies, Merck (MSD outside the United States), and Bristol-Myers Squibb, now have a virtual monopoly on approved and candidate anti-PD-1 agents. Partners Merck KGaA and Pfizer are present in the space, as is AstraZeneca with its R&D arm MedImmune, and Roche/Genentech — all with their anti-PD-L1 drugs, though all lag behind. But the question of why most patients fail to respond to this backbone IO therapy has taken center stage in oncology research and kept the concept of therapeutic combinations alive.

These days, even if an oncology drug in development has no claim to being a stand-alone immunotherapy, the developer will likely attempt to position the asset as

having potential complementary effects in an IO combination. And most often, the target combination will include anti-PD-1. No wonder, then, that the IO space seems preoccupied at the present with this question: What agent or agents will rise to the top as the best complements to anti-PD-1?

For the answer, though, you might have to watch only one company — Merck. Since Merck won the first FDA approval for its anti-PD-1 drug Keytruda (pembrolizumab) in 2014, it has thrown itself headlong into the IO field, buying up assets and launching an ever-lengthening list of clinical trials — most not paid for by Merck — to test the drug in a wide variety of combinations. No other IO-focused company matches Merck in the extent of partnerships and trials.

Why? Roy Baynes, head of global clinical development and chief medical officer at Merck Research Laboratories, has described how his team is building a "data wall" with the multitude of Keytruda combination trials. The trials reflect another trend in the industry's IO development — they steadily expand the products' target indications into almost every cancer type. Merck appears to believe, by January 1, 2018, it will have amassed so much data on Keytruda alone and in combinations, no other company will ever be able to climb over the wall to compete with its anti-PD-1 position.

"Baynes is absolutely correct," says Dr. Llew Keltner, president and CEO of Epistat, who moderated our original virtual roundtable. "Merck has already won the early and mid-game because it is doing so many more combination trials than anyone else. It is doing the combination trials not because it's trying to find out what companies to buy — it's doing the trials because it wants to see what works. Treatments that work and can get approved in combination with Keytruda will increase Keytruda sales."

People at AACR may well have been distracted from Merck's onslaught by the buzz over IDO inhibitors, a class that has been one of the star candidates for improving response rates in checkpoint blockade. IDO (indoleamine-2,3-dioxygenase) is a "rate-limiting" enzyme in the tryptophan (TRP) to kynurenine (KYN) metabolic pathway, which keeps a lid on immunity.

This year, inhibiting IDO became the new great white hope in IO, and researchers presented multiple preclinical models at AACR supporting the concept. A Phase 2 trial by NewLink Genetics of its tryptophan metabolic pathway drug, indoximod, in combination with Keytruda, even generated some disappointment when its interim results showed "only" a 52 percent overall response rate (ORR) — 6 points lower than the ORR in Phase 1 results by a combo of Keytruda with Incyte's anti-IDO drug, epacadostat. Incyte echoes Merck's strategy of multiple partnerships and trials to amass data on its IO candidates in a variety of combinations. It has partnered with both Merck and BMS to conduct trials of their products in combos with epacadostat.

Among the Big Pharma IDO contenders, Pfizer is playing catchup in the class, in a deal with iTeos now at the Phase 1 stage in brain cancer. But Pfizer is also catching up in IO generally. After spending more than $3 billion for avelumab (Bavencio), an anti-PD-L1 drug and candidate for urogenital cancer, the company — with codeveloper Merck KGaA (EMD Serono) — won an FDA approval for the product in March 2107, but only in the rare indication of Merkel cell carcinoma. AstraZeneca/MedImmune have an extended IO development program, but only one approval so far, for NSCLC candidate Imfinzi (durvalumab), in treating locally advanced or metastatic urothelial carcinoma (mUC). And Roche's anti-PD-L1 atezolizumab (Tecentriq) recently failed unexpectedly in a Phase 3 urogenital cancer trial, adding fuel to the fire of speculation — long overdue — about the potential differences in mechanism of action and clinical response between different molecules in the anti-PD-1/PD-L1 class.

ANGLES OF PROGRESS

As clinical trials sort out the immunotherapy combinations empirically, two normally separate sectors, academia and industry, have joined the basic and preclinical research hunt for mechanistic understanding. The clinical progress of the past year has ironically revealed the lack of commensurate progress in probing the many factors that influence immunity at the level of cells, molecules, and the tumor microenvironment — one big avenue of hope for improving clinical response rates. Enumerating the relevant biomarkers alone is not enough; the pathways and junctions in the system interact, like the parts and pieces of a living reactor, to create the complex tug o' war between immune activation and regulation.

The immune system is a metabolic system, where communication is usually not binary but comes in information-rich packages such as proteins. Academic and company scientists are working — sometimes separately, often together — to see the dynamic interaction inside immunity at a higher and higher resolution. The driving force behind the intense investigation and collaboration at the mechanistic level is the strong belief the efforts will lead to answers about how different patients respond to treatment and what treatments could make all patients respond better.

It would be a mistake, however, to see up-regulation of one immune component or cell type as always "good"

and down-regulation of another component or cell type as always "bad." An immune system activated by checkpoint blockade will express immuno-inhibiting components to regulate immune response. Under the spell of a tumor, Tregs may help defeat immune response, but working as part of an effective response, Tregs keep immunity from raging out of control and attacking healthy tissue. Right now, perhaps thousands of studies in academic and industrial settings are creatively resolving this moving micro-universe of immunity at a finer and finer grain. Clinical results are driving this quest for a more refined theory and structure as a basis for predicting which new therapeutic approaches might improve the results.

"Some of the cases of resistance to checkpoint blockade are ones where the innate wiring mechanisms of the immune system are actually being mutated or altered, which is a bit worrisome," says Lawrence Fong, M.D., of UCSF. An original member of our virtual roundtable, Fong and his associates are leading clinical researchers in IO. "The mutations show the ability of the tumors to evade the immune response. That means we really need to think about multimodality therapies, including other therapeutic approaches that may not be dependent on that wiring of the immune system. There are not only ways to target the cancer cells through conventional means, but also other immunotherapeutic means that are not dependent on that signaling mechanism."

One of our KOLs believes the most powerful lens for the job is genomics. "There is a lot of research into how and why IO works in some patients but does not work in others, which is very promising," says Tim Greten, M.D., of the National Cancer Institute. Greten has been a participant in this series from the beginning and continues to conduct groundbreaking IO research at the NIH. "We are finally giving more and more attention to the correlation of genomics and immunotherapy — understanding the biology and how genes may affect immune responses, and how we can potentially combine genomics and immuno-oncology to prescribe the best therapies or therapeutic combinations for each patient. What I would like to see in oncology is for geneticists to get together with immuno-oncologists."

"It's extremely important to continue our research, because we need to understand mechanisms of action and we need to understand the pharmacodynamic effects of these combinations," says Wolchok. "We need to know how the combinations are hitting their intended targets and then focus those particular combinations on particular subsets of patients who have a need for that specific combinatorial approach. We are really striving to understand how to make immunotherapy combinations a more precise intervention. There is a whole other world of trials combining checkpoint blockade with other forms of anticancer therapy, whether they be targeted therapies, chemotherapy, radiation therapy, or other means of local tumor destruction."

Here stands the state of progress in combination cancer immunotherapy in mid-2017. Further studies and presentations at ASCO will certainly add to this description, but are unlikely to change the basic scenario. Immuno-oncology now rules oncology, and IO must now catch up to itself with intensified mechanistic and clinical research in a grand collaboration of academic and industry science. L

KEY OPINION LEADERS SPEAK

The following key opinion leaders in immuno-oncology and past participants in our cancer immunotherapy series contributed to this article. Special thanks to our virtual roundtable moderator in the series, Dr. Llew Keltner.

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President and CEO, Epistat

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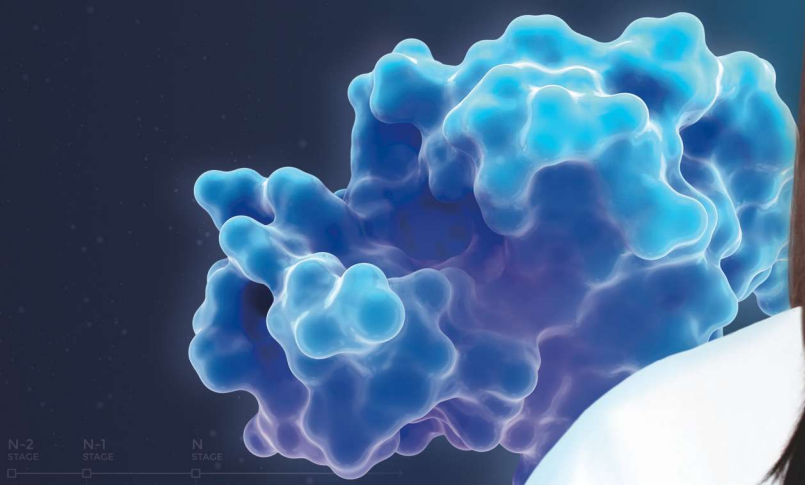

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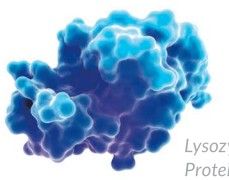

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Genentech Masters Breakthrough Therapy Designation

ED MISETA Chief Editor, Clinical Leader @EdClinical

Genentech has garnered 15 Breakthrough Therapy Designations for its medicines since 2013, which is more than any other company. Jeffrey Siegel, senior group medical director for Genentech, believes this success reflects the company's focus on developing new approaches to address unmet medical needs.

It also makes him a bit of an expert in understanding the intricacies of the FDA program. Siegel was with the FDA for 14 years before joining Genentech and has devoted most of his career to facilitating the development of products to address unmet needs.

"I think the best way to understand the benefits of Breakthrough Therapy Designation is to think about what companies hope for when they approach the FDA with a new product and what they fear might happen over the course of the process," he says. "What companies generally hope for is that they'll be able to get concurrence with the FDA on design of the trial, and specifically about the primary endpoint that would determine success or failure of the study. Companies want to know their approach will stand up to the scrutiny of an FDA approval."

Unfortunately, that process does not always go as planned. When it doesn't, reaching agreement with the FDA on the design and conduct of the study can be a lengthy and time-consuming process. Just scheduling a meeting with FDA to get feedback can take a long time. Fortunately, this is where Breakthrough Therapy Designation can help.

The designation is a special status the FDA confers on programs believed to address an unmet medical need. This can be a product that has shown benefits in a disease where there are no approved therapies, or it can involve a therapy where data indicates the efficacy is over and above the best available approved therapy.

"For Breakthrough Therapy Designation to apply, clinical data is required to support the efficacy bar set by the FDA," says Siegel. "In other words, if you have really good data from animal models or other preclinical settings, that's great. But it won't get you Breakthrough Therapy Designation. There has to be patient evidence that the treatment provides a particularly high level of benefit."

DESIGN PROPER ENDPOINTS

When the FDA grants Breakthrough Therapy Designation, it will bring in senior management to assist the sponsor in moving the medicine forward in the quickest manner possible. The FDA agrees to have meetings when the company requires interaction. The designation also means the sponsor gets expedited review once the package is submitted for approval. This could shave several months off the standard approval timeline.

When Siegel was with the FDA, he worked on rheumatoid arthritis at a time when the first biologics were being developed. He helped develop an industry framework for what sponsors would need to show to get approval and demonstrate additional improvement in progression of disease.

"I had a philosophy when I worked at the FDA as a reviewer and clinical team leader," he says. "Occasionally companies would come forward with programs we felt were not acceptable. When that happened, I instructed the reviewer working under me

to always propose an alternative. For example, if the company proposed a laboratory outcome that didn't necessarily correlate with a clinical benefit, I would work with the reviewer to discuss how the company could show a clinical benefit."

At Genentech, he continues to work in many of the same areas, still devising endpoints that will be acceptable to the FDA. His advice when designing endpoints? Always look at things from the other person's point of view. Look at it from the patient's and FDA's points of view. Both will be concerned about showing a clinical benefit, not just a benefit on some laboratory endpoint that may provide a benefit to patients.

"If you have really good data from animal models or other preclinical settings, that's great. But it won't get you Breakthrough Therapy Designation."

JEFFREY SIEGEL
Senior Group Medical Director
Genentech

When devising endpoints that show benefits to patients, there are certain things Siegel says are important to consider, especially when there is no established approval pathway. A medicine might meet a biomarker endpoint that doesn't correlate with clinical benefit. Outcome measures that clearly indicate benefit to patients will generate a positive response from the FDA. When sponsors propose a biomarker as a primary endpoint, they should provide the FDA with persuasive evidence that a change in the biomarker predicts a change in a meaningful clinical outcome.

THE FOCUS MUST BE ON QUALITY

Genentech's 15 Breakthrough Therapy Designations have come at various points in the development cycle. The earliest time a sponsor can receive the designation is when it first has clinical data from patients showing the product benefits over and above available therapies.

According to Siegel, that can potentially be after Phase 1 in certain areas such as oncology. In immunologic diseases it would more commonly occur after Phase 2. Sometimes it may even come as late as the end of a Phase 3 trial. Regardless of when the submission is made, Siegel believes the single most critical factor to getting the designation from the FDA is data quality. That makes quality data the single greatest challenge as well.

In discussing quality, Siegel likes to use scleroderma as an example. Scleroderma is an immunologic disease where patients develop fibrosis of internal organs as well as thickening of the skin. The fibrosis will lead to damage of the lung, kidney, and other internal organs.

"The most common aspect, and the one that is most apparent, is the skin thickening," says Siegel. "That can make it difficult for patients to carry out daily living activities and can lead to disability. When we first started our program of tocilizumab (Actemra) for this disease, we wanted to do a Phase 2 proof-of-concept study. For diseases where there is no clear path forward, a typical Phase 2 proof-of-concept study normally takes the form of an open-label study of, say, 25 patients. The goal is to see if responses in the patient indicate a benefit from the drug."

OPEN LABEL CAN FALL SHORT

With immunologic diseases such as scleroderma, symptoms in a patient will tend to wax and wane. This can create problems for researchers. If you conduct an open-label study in 20 patients and they show improvement, you will not know if there is clinical benefit from the drug, or if that is what might have happened anyway.

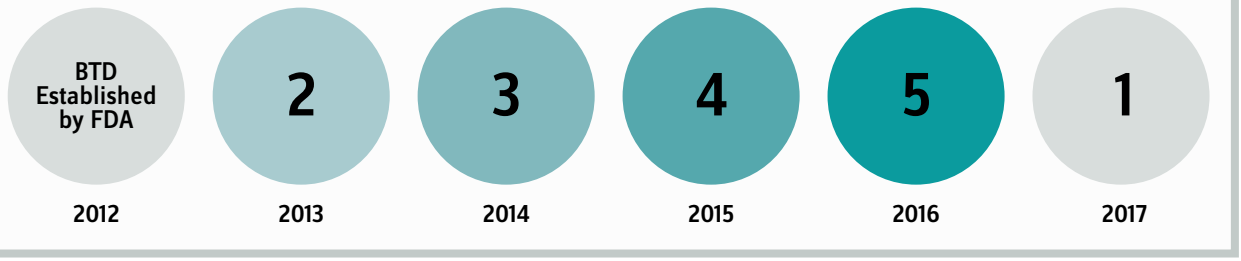
"You want to present FDA with quality data, but this situation can leave uncertainty about success of the study," notes Siegel. "That uncertainty in Phase 2 will also make it more difficult to plan for a Phase 3 study. We were aware of that, so when we began our Phase 2 study we opted to make it a large, randomized trial comparing tocilizumab to a placebo."

Skin score, which has been validated in scleroderma, was used as the primary endpoint. But Genentech also measured exploratory endpoints for scleroderma that would indicate potential benefit for the serious internal organ manifestations. The results were promising for both easing the skin thickening as well as reducing the rate of lung disease progression. The data was presented to the FDA, and the breakthrough therapy designation was granted. The FDA agreed with Genentech that tocilizumab was a promising new therapy for patients.

FDA regulations state the agency approves drugs based on substantial evidence of efficacy. FDA personnel will tell you that typically means data from one or more adequate and well-controlled trials. A blinded,

GENENTECH'S BREAKTHROUGH THERAPY DESIGNATIONS:

(AS OF MAY 2017)



randomized trial provides that substantial evidence. An open-label trial, in some cases, may not.

"Randomized trials allow researchers to see benefits with the study drug when compared to what patients would have experienced if they'd been treated with standard of care," says Siegel. "The FDA accepts that as substantial evidence."

ENSURE SITES ARE TRAINED

In the scleroderma trial, the primary endpoint was what's called a modified Rodnan skin score. To gather the needed data, an experienced investigator will pinch the skin of a patient in many areas of the body. The researcher determines if the skin has normal suppleness that skin ordinarily has, or if it's hard and difficult to pinch.

The test is a validated outcome measure and has been shown to correlate with the amount of fibrosis in the skin. Properly trained investigators in studies have been shown to be able to differentiate people who improved, worsened, or experienced no change.

The other endpoint was the measure of lung progression, calculated using the Forced Vital Capacity (FVC). This is a measure of the capacity for gas exchange in the lung. Scleroderma patients with fibrosis of the lung will have decreasing FVC measures.

While the FVC measure is fairly straightforward, recruiting investigators who aren't adequately trained on the Rodnan skin score can create problems. The test needs to be conducted in a uniform manner so as to generate successful readouts at the end of the study.

"To get high-quality data, we do everything possible to create uniformity among the investigators," states Siegel. "In the case of scleroderma, this is particularly important. A researcher in Paris and another in LA might perform the same pinch test for skin fibrosis, but interpret the results differently."

To avoid this possible tainting of data, Genentech brought together the targeted investigators to make sure they were adequately trained on how to properly read patients and to ensure everyone was performing the test the same way.

UNIFORMITY ACROSS STUDY RESULTS

Genentech retained the services of a couple of academic investigators who were expert clinicians and had worked together to standardize the Rodnan skin score. They were able to train investigators on the exact way to apply the Rodnan skin score and make sure everyone was interpreting the results accurately.

"It was a great way for us to get uniformity across our study results," says Siegel. "This is something everyone should be aware of when conducting proof-of-concept studies, particularly Phase 3 studies where you tend to have clinicians in multiple countries. Conducting the training is a challenge, but the rewards you reap are huge."

In conducting the training, a video is often sufficient. That is generally the case if investigators are familiar with the test and have conducted it in the past. The video serves as a refresher on what they need to do. For this study, the expert clinicians were able to offer additional insights to investigators. To ensure everyone had an opportunity to interpret the results, the clinicians also brought in patients who were willing to participate in the training.

"The patients would meet with individual clinicians who would then perform the same tests," adds Siegel. "They were asked to score the hands, arms, chests, and legs. The experts then checked to see if all clinicians scored each of those body parts the same way."

Some discrepancies were noted. When that happened, the clinicians were brought together to talk about how they were scoring patients. A consensus was reached on how to apply standardized criteria to see that all patients were scored the same way.

"By bringing good science, quality data, and a focus on unmet medical need to the FDA, companies can make major advancements in unmet medical needs," adds Siegel. "Attaining a Breakthrough Therapy Designation might require some additional insight and work, but by working with the FDA in this manner, we will be able to bring our therapies to patients more quickly and efficiently." L

Commercializing an orphan drug requires designing solutions to improve the treatment journey. In-home inventory management solutions combined with sophisticated logistics expertise makes participating in a clinical trial more convenient, easing recruitment and reducing withdrawal rates. Increasing patients' access to treatment, improving adherence, reducing costly emergency visits, and enhancing the quality of life for both patients and caregivers takes high-tech solutions and high-touch patient support. It takes a committed commercialization partner. It takes AmerisourceBergen.

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Is The Cuban Biopharma Industry A Forerunner Of Pharma 3.0?

Part 2

ANDRÉS CÁRDENAS-O'FARRILL

Part one of this article ran in our April issue and explained how Pharma 3.0 focuses on health outcomes and stresses open collaboration platforms and long-term partnerships with nontraditional players in order to gain access to underserved markets. The article also explained how Cuban biopharma is part of a broader plan and how the regulator's role within the industry is a key aspect of these broader integration efforts.

PRIMARY CARE AS BIOTECH'S ASSESSMENT TOOL

Constraints imposed by the U.S. embargo have hampered Cuba's healthcare funding and access to mainstream medicines and technologies. Thus, the island's health policy emphasizes basic primary and preventive care, addressing diseases and problems before they can become major issues.

Equally important, primary care also has provided a formidable backbone for biomedical research, enabling massive informed-consent participation in clinical trials of new medications and vaccines. Likewise, it plays an important role by collecting community-based information about specific clinical and epidemiological patterns affecting each region. This allows the creation of comprehensive national records that help determine which health issues pose the greatest risk to society. This information, in turn, contributes to better allocation of resources to deal with risk and channels the sector's creativity in ways that lead to more socially productive innovation. It is more humane, faster, and cheaper. It is also astoundingly similar to the patient rapprochement mechanisms included in the new holistic approach envisioned by Pharma 3.0.

This commitment to primary and preventive care started during the 1960s when the government established a system of integrated community clinics (polyclinics). Cuba's medical facilities remain focused on primary care, with family medicine required as the first residency for all physicians.

This organizational structure has made it possible for the innovative diagnostic tools developed by the industry to be quickly integrated into the health system through primary care services. This is the case of SUMA technology (a screening system designed to solve the country's needs for diagnostic technology), which is an indissoluble element of several programs of Cuba's healthcare system. In fact, these programs are related to a network of diagnostic laboratories and screening centers available in each municipality of the country. This is also the case of CIMAvax-EGF, which is an innovative therapeutic cancer vaccine (currently under clinical trial in the U.S.), whose approval and assessment in Cuba have had family doctors and primary care facilities strongly involved.

SHARING HEALTH INFORMATION TECHNOLOGY, DATA

The economic crisis at the beginning of the 1990s had devastating effects throughout Cuban society. One of the most affected activities was the exchange and updating of specialized information for healthcare researchers. Resources for academic and practitioner-related knowledge (e.g., books) were scarce, so health information professionals came up with a creative way to solve the problem: INFOMED.

INFOMED was founded in 1992 as the Cuban National Health Care Telecommunications Network and Information Portal. Healthcare innovators created a digital infrastructure to support healthcare information,

using computers to establish a virtual space for exchange among research institutes, medical faculties, primary care institutions, hospitals, and eventually with the international scientific community.

This innovation contributed to one of the key goals of Cuban biotech by providing a platform for continuous data collection, analysis, and dissemination within the system, while simultaneously reducing costs. When Cuba connected officially with internet in 1996, the flow and exchange of information exploded. In 2002, INFOMED was awarded the Stockholm Challenge Prize in the health category for life-improving information technologies.

> *"Cuba has still been able to produce a huge number of innovative and affordable drugs to tackle diseases that run rampant in low-, middle- and even high-income countries."*

THERE IS, INDEED, A SIMILITUDE

Given the above, the idea of the Cuban biotech as a forerunner of Pharma 3.0 doesn't seem that far-fetched. The notions of engaging with patients, developing ongoing relationships with them and collecting their data with their informed consent, identifying target populations, focusing on prevention and data sharing, and so on have long been crucial features of Cuba's biomedical complex. This commitment to prevention, integration, and collaboration has turned out to be an opportunity for both innovation and high-quality healthcare delivery.

Of course, there is no room for romanticizing here. The Cuban healthcare system is a gigantic task carried out by a poor country under extraordinarily tight conditions. It is not a perfect system (there is no such system). Particularly in the last decade, some critics have noted their dissatisfaction with issues such as material shortages, inefficiencies, and low wages, all of which are compounded by the constraints imposed by the U.S. embargo. Despite these issues, Cuba has still been able to produce a huge number of innovative and affordable drugs to tackle diseases that run rampant in low-, middle- and even high-income countries.

The story of the Cuban biopharmaceutical industry provides a remarkable example of how openness, long-term care, and integration can save significant time and cost. This has finally begun to be recognized by the movers and shakers of the pharmaceutical industry worldwide. Welcome Pharma 3.0, but please remember the Cubans. L

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

Awakening The Biotech Entrepreneurial Spirit

CAMILLE MOJICA REY Contributing Writer

Roger Newton still remembers the day in November of 1997 when he tripped over a pile of books in a Borders Bookstore in Ann Arbor, MI. He looked down on a back cover of one of the books to see the words: "Don't let your company kill you." He turned the book over and saw the title of Robert E. Quinn's book, Deep Change: Discovering the Leader Within. *His life and career would never be the same.*

When Newton met with Quinn two weeks later, he had already been contemplating leaving Warner Lambert/Parke-Davis due to an unpopular reorganization. He had been working there for 17 years and was the codiscoverer and product champion of Lipitor, the best-selling prescription drug ever. "My working situation reached the point where I couldn't do the science I loved to do," he explains. What Newton hadn't decided was what to do next. The conversations with Quinn made it clear that it was time for him to move on and start his own company. "He turned me inside out to see what I was made of, asking me very deep questions about myself. In the end, he said 'I think you are ready to move on, and you're ready to do something greater than what you have done before.'"

In July of 1998, eight months after meeting Quinn, Newton started Esperion Therapeutics. He did so with Quinn's teachings in mind, vowing to run a positive organization as opposed to a conventional one that is hierarchical and fear-based. It was a professional rebirth that Quinn says is more common than you might think. "In the process of answering those deep questions, something happens to a person. They finally face the truth about their frustrations and decide to take the risk of moving forward," says Quinn, who is cofounder of the Center for Positive Organizations (CPO) at the University of Michigan's Ross School of Business. Quinn is also a pioneer in the field of positive organizational scholarship.

CPO's mission is to inspire and enable leaders to build high-performing organizations that bring out the best in people. Quinn says that is possible when a company's stated purpose is to make a positive difference in the world. The purpose must be clearly stated, shared by employees, and be the basis for all decisions made by leadership. "It leads to a very different philosophy, one based on confidence rather than on fear." Employees

> *"First, you will die a slow death if you stay in a situation where you can't do what you love to do. Second, you must be able to walk naked through the garden of uncertainty."*
>
> **ROGER NEWTON**
> Founder of Esperion Therapeutics and codiscoverer of Lipitor

also must feel valued, heard, and supported. Quinn writes about the positive impact of this service mentality on companies and their employees in his blog.

GIVING BACK

Newton vowed that one day he would do for others what Quinn had done for him. Today, he fulfills that promise as an executive in residence at the CPO and has spent two years giving lectures, counseling students, providing scholarships for students with financial needs, and working with faculty and staff on a three-year strategic plan for the center. Over the years, Newton continued to turn to Quinn for his advice and counsel. Following 9/11, the nation experienced an economic downturn. In March 2002, Newton was forced to lay off 25 percent of his workforce. Quinn and his colleagues conducted workshops for the remaining employees. "They came in and helped me rebuild the company." Newton also says he is indebted to Quinn for his willingness to give his time, energy, and knowledge to help make Esperion a success. "He never asked for anything in return," Newton says.

In 2003, five years after starting Esperion, the company published a study that showed its drug, ETC-216, successfully reduced the plaques that cause heart disease. Those findings were the impetus for why Pfizer paid $1.3 billion to purchase Esperion in 2004. It was the largest payment for a Michigan-based biotech company at the time. It was seen as a largely defensive move to protect torcetrapib, a drug that also raised HDL (the good cholesterol) and had combined with Lipitor to extend its patent life. The combination's failure led to a loss of $1.2 billion and the shutdown of Pfizer's R&D operations in Michigan (see our article on Michigan's life sciences industry in the April 2017 issue). Among the 2,400 people who lost their jobs were the 60 people working at Esperion.

STARTING OVER

Newton found himself sitting in a newly renovated, state-of-the-art, 60,000-square-foot research facility in Plymouth Township, Michigan, alone except for a security guard. In May 2008, he negotiated with Pfizer to buy back the Esperion Therapeutics name and two patents so that he and his "sweat-equity team" of eight people could work together again. At the same time, he was part of a public/private partnership that worked together to buy the newly refurbished building from Pfizer, which later became the Michigan Life Sciences and Innovation Center. "Esperion 2.0" became MLSIC's first tenant, moving into the building in October 2008 — two weeks before the U.S. economy crashed.

Making it through the recession was a challenge, but the new Esperion did not just survive, but has thrived, graduating from MLSIC four years ago. The company is now headquartered in Ann Arbor, MI, and has its first product, bempedoic acid, in Phase 3 clinical trials.

Newton, who now serves as scientific advisor and board director at Esperion, says what he learned from Quinn helped him to both start and restart Esperion. More importantly, he is proud of the company and its achievements. "What we accomplished with a small, productive team of talented and inspired people was remarkable."

Newton says he has learned many lessons during his 35+ years in the industry, but he now shares his experience with new entrepreneurs at the CPO. He reminds them that it takes more than bright ideas to raise the money needed to start and grow a company. "I invest in people first and their technology second," he says. Newton also tells them that they must have mentors, build diversified teams made up of talented people, and have a focused entrepreneurial vision. "You have to have passion, meaning, and purpose for what you do every day to create a positive business environment where your colleagues can thrive in their work and grow personally and professionally." L

"Newton found himself sitting in a newly renovated, state-of-the-art, 60,000-square-foot research facility in Plymouth Township, Michigan, alone except for a security guard."

To read more about Roger Newton and how he helped keep pharmaceutical jobs in Michigan, check out the article "State Funding Fuels Michigan's Life Sciences Industry" in our April 2017 issue.

How NYC Is Building A World-Class Life Sciences Hub

MIKE GOODMAN Contributing Writer

A life sciences ecosystem is taking root in New York City that in 10 years' time could vie with Boston and San Francisco as measured by the number of jobs and startups, funding resources, or high science ideas.

NYC's existing assets are in many ways superior to other life sciences clusters: its research base of academic medical centers is larger than Boston's, it is surrounded by Big Pharma and Big Biotech, it has access to capital from public and private sources, and it can draw from a deep pool of seasoned entrepreneurs and the largest bioscience workforce in the country. Moreover, it has approximately 100 disease foundations, with many having extensive experience in research and investment.

A statistical picture hints at New York's recent growth: Life sciences job growth in Greater NY has been increasing at about 3.3%/year, outpacing San Francisco and Boston. New York is second to California in total active clinical trials, and tied with Massachusetts for second place in NIH basic research grants (2016).

New York's life sciences ambitions have been stymied in the past by the absence of an early-stage VC population and the high cost and low availability of wet-lab space. But there is evidence in the past two years that these hurdles are being met, and the emergence of a handful of homegrown VC-backed startups (see "Venture Capital" section on next page) is the surest sign that something is afoot in NYC.

MEETING ITS CHALLENGES

INVESTMENT. NYC is unique in having numerous, highly incentivized stakeholders who join in diversified syndicates to support early-stage science. Stakeholders include city and state government, local Big Pharma and Big Biotech, philanthropic donors and private funds, and leading academic research centers.

For instance, in March 2015 the New York City Economic Development Corporation (NYCEDC), along with strategic investors Celgene, Eli Lilly, and GE Ventures, announced a $150 million public-private funding initiative to identify and invest in NYC's most promising research and to create startup companies to advance it. The investors brought in two elite early-stage VCs to manage the funds and the startups: Flagship Ventures and Arch Venture partners.

In October 2016, the heads of Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center, Rockefeller University, and Takeda Pharmaceutical Company — collectively known as the Tri-Institutional Therapeutics Discovery Institute (TDI) — and the investors Bay City Capital and Deerfield Management announced the creation of Bridge Medicines. Bridge will take in research projects accepted into the TDI and provide financial, operational, and managerial support to translate them into clinical trials.

LAB SPACE. Euan Robertson, SVP and COO at NYCEDC, says that beginning in the mid-2000s, the NYCEDC joined with Alexandria Real Estate Equities to create the first commercial wet-labs in NYC. The Alexandria Center for Life Sciences provides 1.1 million square feet of office and lab space, "almost the totality of commercial lab space in NYC at the moment."

Since then, other initiatives have further expanded lab

space in NYC. NYCEDC partnered again, this time with Sam Sia, Ph.D., an entrepreneur and faculty member at Columbia University's Dept. of Biomedical Engineering, to develop Harlem Biospace, an incubator providing 2,300 sq. ft. of wet-lab space, equipment, and business support to up to 24 early-stage life sciences companies.

New York's city and state governments have been actively supporting the growth of life sciences through investment, land use policy, and tax incentives. Government is attracted to the tax receipts, the high-wage jobs, and economic diversification. In January 2017 New York Governor Andrew Cuomo allocated $17 million from his recently announced $650 million initiative to support the development of the life sciences in New York State. The $17 million will go to creating a biotech incubator at the New York Genome Center in partnership with Johnson & Johnson's JLabs (part of J&J's global Innovation Center network for nurturing nascent science). JLabs will occupy 30,000 square feet at the NYGC.

Nate Tinker, executive director of New York BIO, says that J&J is doing somewhere between 10 to 20 deals per year in NYC. "Big Pharma is spending a lot of time and venture money in NYC."

Alexandria Real Estate Equities struck again in February 2017 with Alexandria LaunchLabs located at the Alexandria Center for Life Sciences campus. LaunchLabs provides affordable wet-lab and office space for early-stage life sciences startups. Companies selected for LaunchLabs have access to seed-stage capital from Alexandria Venture Investments.

Robertson points out that NYC is still far behind Boston with its 13 to 18 million square feet of commercial lab space. But he's confident that in 10 years' time the gap can be closed.

VENTURE CAPITAL. Robertson notes that the number of VCs active in NYC has sharply increased over the past two to three years. Not only are out-of-town VCs like Bay City Capital, Flagship, Arch, Lux, and Polaris sniffing around NYC for untapped science, but NYC-based firms like Deerfield Management, Versant Ventures, New Leaf Venture

Partners, Accelerator Corp, and Alexandria Venture Investments are also active.

Moreover, local and national Big Pharma has been actively scouting in NYC and recently participated in significant series A financings for homegrown NYC startups Petra Pharma ($48 million), Kallyope Inc. ($44 million), and Lodo Therapeutics ($17 million). Although angel investors and Big Pharma, as well as New York City and state governments, have been reliable investors in NYC life sciences, a VC population is the necessary and, as yet, missing ingredient. VCs not only provide risk capital to young companies, but as importantly, they bring focus and management expertise.

AN ECOSYSTEM THAT SPREADS OUT FROM MANHATTAN

Even today, promising ideas bubbling up from NYC labs are whisked away by out-of-state VCs, or else the startups pick up stakes and leave for Boston or San Francisco. Tinker estimates that until recently "80 percent of the science originating in NYC and that gave birth to startups left within five years for Boston, San Francisco, or Texas."

"We see scope for life sciences growth outside of Manhattan."

EUAN ROBERTSON
SVP & COO
New York City Economic Development Corporation

Robertson starts from the premise that a life sciences ecosystem generally tends to grow from a center of gravity. "In NYC that's Manhattan. It's the First Avenue corridor of academic medical centers, the Alexandria Center for Life Sciences on the East River. Most startups, particularly those focused on therapeutics, want to be located near those institutions." As companies mature, he says, particularly as they become fully integrated companies doing large-scale manufacturing, "we see scope for life sciences growth outside of Manhattan." Diagnostic or device companies may be first to move since proximity to NYC medical centers isn't as necessary as it is for therapeutics-based companies. NYCEDC, being a city agency, sees the boroughs of NYC as the natural place for them to locate, but allows that New Jersey and Philadelphia, investing in the infrastructure left by a contracting pharma industry, could also absorb more mature companies. "We view these as complementary investments in a connected ecosystem," says Robertson.

NYCEDC appears to have recently adopted the evolutionary view of an industrial ecosystem's growth over time, spreading out from Manhattan. In 2010, NYCEDC and SUNY Downstate announced the development of BioBAT, 500,000 square feet of commercial biotech space in the Brooklyn Army Terminal in Sunset Park, Brooklyn. The investment may have been premature; as of this writing, few biotech companies have moved in.

It's still unclear if NYC can build out its wet-lab capacity to accommodate all the VC-backed startups that will be generated in the coming years. With a larger medical research base than Boston, laboratory capacity would have to be roughly 25 million square feet to process all the ideas coming from NYC's basic research community. And although there's been an uptick in early-stage VC activity, many of the investors are based out of state. When others like Third Rock and Atlas Ventures become involved, and moreover commit to establishing fully staffed offices in NYC, we'll know that VCs are serious about mining NYC's medical research.

NYC is engaged in a brave urban experiment. By building on its extraordinary assets, it proposes to close the gap with Boston and San Francisco within the decade. Its city and state governments are behind the effort, and VCs seem to have recognized the opportunity. According to Tinker, even the tech transfer offices at Columbia University Medical Center, NYU Langone Medical Center, Weill Cornell Medical College, and Rockefeller University have internalized a NYC economic development mission and are looking in their own backyards instead of licensing their inventions outside NYC to the highest bidder. Clearly the NYC life sciences ecosystem has arrived at an inflection point; now everyone is waiting for the next step. L

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Bridging The Gap Between Academia, Small Biotechs, And Industry

SUZANNE ELVIDGE Contributing Writer @suzannewriter

Academia and biotech have long been sources of innovation for the pharmaceutical industry, and this is increasingly important for Big Pharmas that want to prop up flagging pipelines or boost particular areas of focus. Some of the large pharma companies have started to reach out to academia through formal programs, such as GSK's Discovery Partnerships with Academia (DPAc), or Merck's support of the California Institute for Biomedical Research (Calibr). However, academia, research institutions, and small biotechs can find it challenging to reach back the other way and get their voices heard by pharma companies and bigger biotechs.

The role that biotech and academia can play in bridging the gap was discussed at the BIOPROSP_17 8th International Conference on Marine Biotechnology, held in Tromsø, Norway, in March 2017.

ACADEMIA: ATTRACTING COMMERCIAL PLAYERS INTO PARTNERSHIPS

Academic researchers have an excellent track record in being innovative, but getting those innovations to market has proved difficult, leaving promising potential drugs languishing in the so-called valley of death. Also described as the translation gap, this comprises the stages between drug discovery when researchers have an interesting candidate on the bench and efficacy trials at Phase 2 or Phase 3 where a drug's value can be proven.

According to Asbjørn Lilletun, Norinnova Technology Transfer, Norway, one of the difficulties faced is the difference in approach to research. "Innovation in academia is not the same as in business. There needs to be a balance between the open nature of research in academia and the intellectual protection needed in the pharma industry — and between the long-term nature of academic research and the need for speed in industry."

To succeed in creating projects that attract the attention of pharma industry business development teams, universities and academic researchers need to be aware of the market needs. Technology transfer offices can play a role here by providing a more commercial mindset and giving access to networks, funding, and potential partners. An example of success is MARBIONC — Marine Biotechnology in North Carolina — which is based at the University of North Carolina Wilmington (UNCW) and discovers, develops, and markets new products and technologies derived from the sea.

"MARBIONC was created to stimulate economic development and marine biotech in North Carolina," said Andrea Bourdelais, research associate professor at the Center for Marine Science at UNCW. "A slice of the money from any marketed products goes back to the labs."

The MARBIONC group identifies the markets to ensure that any products created meet specific needs, and then the group creates teams of people from science, business, and academia supported with a preexisting infrastructure. As an example, Silurian Pharmaceuticals licensed brevenal, a potential treatment for cystic fibrosis, from MARBIONC.

Creating partnerships is important for the future of research in academia, as funding is increasingly dependent on evidence of collaboration. It is important, however, that academic researchers remember that

they need to bring value to the partnership and not just create a partnership in order to get a grant.

"Companies and universities need to focus on quality in research, and this is helped by long-term partnerships supported by an increased focus on open innovation," says Lilletun.

"There needs to be a balance between the open nature of research in academia and the intellectual protection needed in the pharma industry."

ASBJØRN LILLETUN
Norinnova Technology Transfer
Norway

NETWORKING AND SHARING TO BRIDGE THE RESOURCES GAP

It's not just academic research organizations that find the gap between discovery and the clinic a challenge; this can be a difficult step for startup companies, too. Catapult Life Science, through its Life Science Pilot, is using networking to create a resource pool for smaller companies to help them take the next step.

"There is a gap between early-stage R&D in universities, biopharma clusters, and research parks and the late-stage development and commercialization by bigger companies," said Astrid Myrseth, CEO at Catapult Life Science, Norway.

The Life Science Pilot network is linked with the newly established and Oslo-based The Life Science Cluster (TLSC), which is a service center that provides access to equipment, infrastructure, and industry experience. The network aims to connect people with skills from a common resource pool.

Njorth Bio, based in Tromsø in Norway, also focuses on using shared resources to commercialize innovative bio-based ideas, but takes a rather different approach, as Jessica Green, business developer, explains. "We work with researchers who have a good idea, but their research institution or technology transfer office is not interested."

Njorth Bio's business model is similar to that of a technology transfer office, but rather than launching a company, Njorth Bio licenses the idea and wraps it into one of its three existing daughter companies, Njorth Bio_boost, Njorth Bio_trim or Njorth Bio_cure, depending on the area, and provides access to a pool of shared resources. This reduces risk for the inventor and cuts costs because the infrastructure already exists.

PHARMA'S DEMANDS AND EXPECTATIONS FROM PARTNERSHIPS

As Erik Hjelvin, medical director, Pfizer, Norway, explained at BIOPROSP_17: "R&D efficiency is falling despite tremendous increases in research. It takes between 5,000 and 10,000 compounds in drug discovery to create one drug, and 75 percent of the cost of a new drug is based on the failures."

Pfizer's solution to this challenge is through partnerships, including those with Big Pharma, biotech, disease foundations, and academic partnerships. As well as bringing along development capabilities for its partners, Pfizer also can provide funding through its venture capital arm, Pfizer Venture Investments. However, Pfizer and other pharma companies have to come into partnerships with academia and startups with specific demands and expectations.

"We ask that our potential partners understand our focus areas and have a common strategic interest and an interest in cooperation. They should be able to provide us with a defined contact person who has the authority to discuss and disclose an up-to-date non-confidential presentation," says Hjelvin.

CREATING A GOOD AGREEMENT

A solid agreement is a crucial part of a partnership, as Theresa Comiskey Olsen, a partner at Langseth Lawyers, Norway, explained at BIOPROSP_17. "The draft agreement needs to balance benefit and risk and should be a win-win for both parties," she said.

To create a good agreement, the parties need to establish trust and should communicate what is important and why up front. This includes an awareness of the benefits and questions of exclusivity, semi-exclusivity, and nonexclusivity. For example, they should know:

- Is there a right to sublicense, or would rights return to the technology owner?
- If the licensee makes improvements to the invention, will these have to be licensed back?

The intellectual property rights also need to be considered, such as patents, knowhow, and field of use, including any improvements and new developments. "When creating an agreement, both parties need to be aware of the details, and plan ahead for any likelihoods," said Comiskey Olsen.

Amorsa's Self-Funded Path To Big Pharma Partnerships

CAMILLE MOJICA REY Contributing Writer

By some estimates, it costs about $10 million per year to operate a startup pharmaceutical company. Funding that traditional path usually involves obtaining nondilutive grant funding, then angel investment, followed by a Series A round, and, if all goes well with the science, a strategic partnership with a large pharmaceutical firm to develop the company's lead compound. Increasingly, however, pharmaceutical entrepreneurs are creating new ways of skipping some of these steps — ones that cost time, money, and ownership stakes in their own companies.

Amorsa Therapeutics has accomplished something rare — if not unheard of — by skipping these steps entirely. The company, founded in 2013, was self-funded for three years before entering into a strategic partnership with Janssen Pharmaceuticals in January 2017. This journey was made possible by industry experience, scientific expertise, and rock-solid confidence in their choice of therapeutic target. "We never lost the confidence that we were going to make this happen," says Joe Blanchard, Amorsa's CEO. "Ultimately, we were rewarded with a high-profile partnership that bolsters our confidence even further."

Amorsa's lead drug candidate is an orally delivered therapeutic for treatment-resistant depression (TRD) based on its proprietary ketamine analog technology. Ketamine is a drug approved by the FDA in the 1970s for anesthesia that is administered intravenously. The company's novel small molecule candidate is designed to show efficacy as a rapidly acting antidepressant with an extended duration of action. It is administered orally and is expected to have an attractive side-effect profile.

INDUSTRY EXPERIENCE

Amorsa's cofounders knew they had the industry know-how to take a therapeutic from idea to market. Combined, they have 75 years of experience in both large multinational pharmaceutical corporations and startups. "We were willing to forgo salaries for the first three years of the company's existence," Blanchard says. He estimates he and his two cofounders invested $2 million to $3 million in Amorsa over that time, including "payments in kind" to founders and consultants. "Overall, our approach to date has been very capital-efficient."

Amorsa began as a virtual startup, a cost-saving strategy that is increasingly common. No lab or office space means no overhead. Office work is done from home. Data needed to raise funds and move a product further down the pipeline is generated by CROs. Amorsa outsourced its studies to specialized CROs, including one cofounded by Alex Nivorozhkin, Ph.D. Nivorozhkin serves as the company's COO. He and Michael Palfreyman, DSc., Ph.D., the company's CSO, were the ones who came to Blanchard with the idea of creating oral forms of ketamine analogs for treating depression, pain, and other CNS disorders.

CHOOSING KETAMINE

There are two limitations to widespread use of ketamine that Amorsa set out to address. First, it can have unusual side effects, including out-of-body sensations. Importantly, Amorsa identified technical approaches that it believes can solve this problem. "The scientific

evidence is clear that ketamine's active metabolites significantly contribute to its therapeutic effect and potentially have an improved side-effect profile," Blanchard explains. The other problem is that ketamine is administered intravenously. One of Nivorozhkin's specialties happens to be formulation chemistry. "We knew we had the expertise to address this challenge and formulate our drugs into oral products."

ABANDONED BY BIG PHARMA AND VCs

Choosing to develop a therapy for depression, however, had big drawbacks. Amorsa's founders were well aware that development of psychiatric drugs has been virtually abandoned by large pharmaceutical companies. In 2012, Steven Hyman of the Broad Institute of MIT and Harvard published a commentary in *Science Translational Medicine* in which he reported that most major pharmaceutical companies had cut or eliminated R&D funding for psychiatric disorders, despite a vast unmet need and a growing worldwide market. There are various reasons for this abandonment — one being the difficulty in developing treatments with significant improvement over generics. Many Big Pharma companies have shifted their focus to other therapeutic areas, especially oncology and diabetes. "We knew that finding a corporate partner for a new depression treatment wasn't going to be easy, especially in the preclinical stage," Blanchard says.

"We were willing to forgo salaries for the first three years of the company's existence."

JOE BLANCHARD
CEO, Amorsa Therapeutics

Venture capitalists have also stayed away from funding novel therapies for the treatment of psychiatric disorders. According to a 2016 Bio Industry Analysis report, only four of the nearly 300 venture financings in 2015 involved psychiatric pharmaceuticals. Self-funding seemed like the only logical strategy for Blanchard and his colleagues. "We knew that the financing challenge for us would be even greater than for most life sciences startups," Blanchard says. Confidence in ketamine is what kept the team going. "The one thing I've learned is that compelling science will win out at the end of the day. And we've always strongly believed that we have very compelling science and were able to ignore the dire statistics, convinced we would be an exception."

PRECLINICAL PARTNERSHIP

Given the financing environment for startups focused on treating CNS disorders, Blanchard and his colleagues decided to focus on entering a preclinical stage corporate partnership. "We knew this was kind of a "catch-22," since it's pretty rare to pull off a partnership with a top-tier firm without first raising at least a Series A round to advance the lead program." Nevertheless, Amorsa's founders understood that R&D productivity inside Big Pharma organizations remains challenging, and that these companies have been aggressively outsourcing more of their R&D externally, as well as entering into more early-stage deals.

To make Amorsa more attractive to potential partners, the founders invested in several critical de-risking studies to generate data that would hopefully interest companies in a potential early-stage deal.

Fortunately for Blanchard and his colleagues, Janssen is one of the companies that has maintained efforts in the CNS area. Blanchard says he had his eye on Janssen because reports indicated that each year the company licenses more than 50 products and platform technologies. "They were at the top of our target list for a potential partnership." Blanchard identified the team responsible for external R&D and early-stage evaluation of opportunities in neuroscience at Johnson & Johnson, Janssen's parent company. He contacted the business development arm of the company and was put in contact with the neuroscience team. The company was one of 10 still active in neuroscience drug development that Blanchard contacted.

Under the terms of the January 2017 agreement, facilitated by Johnson & Johnson Innovation, Amorsa received an up-front payment, along with research funding, and is eligible to receive preclinical, clinical, regulatory, and sales milestones, plus tiered royalties on product sales. Janssen has been granted a worldwide exclusive option to license one of Amorsa's preclinical drug candidates. Amorsa will manage the preclinical development program, while Janssen will assume responsibility for subsequent clinical, regulatory, and commercial development of the licensed drug candidate.

Amorsa plans to remain a virtual company for the time being. Its founders are also focused on developing a therapeutic for acute pain and are currently seeking to raise approximately $10 million. They are looking at various sources including grants, venture funding, and funding from family offices. They would welcome a strategic partnership, such as the one they have found in Janssen. Given the state of opioid addiction problems facing the U.S. today, the market is wide open for innovative solutions to pain management.

Can DalCor Pharma Succeed Where Others Have Failed?

CAMILLE MOJICA REY Contributing Writer

After the worldwide success of statins, no one expected the epic failure of a class of drugs designed by the biggest names in Big Pharma to double the reduction in cardiac risk seen with statins alone. Statins lowered LDL, the bad cholesterol. The new drugs, called cholesteryl ester transfer protein (CETP) inhibitors, would raise HDL, the good cholesterol. Taken together, the drugs would reduce risk of cardiovascular events by up to 80 percent — or at least that was the idea.

But, one by one, large clinical trials of CETP inhibitors by Eli Lilly, Pfizer, and Roche all failed. (Merck & Co. has a study that is due to report later this year.) Collectively, these companies lost billions racing to bring the first CETP inhibitor to market.

Now, an ongoing 5,000-patient clinical trial that began in April 2016 is testing the CETP inhibitor orphaned by Roche in 2012, called dalcetrapib, on a targeted patient population. The dal-GenE study is being sponsored by DalCor Pharmaceuticals, which secured the worldwide exclusive license to the drug from Roche and raised $150 million in venture funding to conduct the trial.

The rationale for the new study is largely based on a retrospective analysis of 5,749 patients' DNA that was published in 2015. The analysis looked at patients who had taken part in Roche's original trial, called the dal-OUTCOMES study. It was a large, double-blind study which randomized over 15,000 patients already taking statins. In that study, the drug raised HDL by 30 percent, was well-tolerated, but did not reduce cardiac risk. The later DNA analysis showed that the drug did in fact lower cardiac risk by 39 percent in patients who had a specific genetic profile and were taking dalcetrapib.

The current DalCor study enrolls patients who have experienced a cardiac event, are taking statins to lower cholesterol, and who have been screened using a companion genetic test made by Roche Molecular Systems. The task at hand for DalCor's leadership is securing a large industry partner to market and sell dalcetrapib upon successful completion of the dal-GenE study. "We need a partner to begin that commercial process," says DalCor CEO Robert McNeil, Ph.D.

To entice potential partners, McNeil and his core team of five people are focused on reducing the risk that the current trial might fail. They are continuing research that will explain how and why dalcetrapib works in the target population in the hopes of overcoming the stigma of a previously failed pharmaceutical. Their aim is to get the world to see that the personalized genetic approach can be used to treat heart disease in much the same way it is currently used to treat cancer.

REDUCING FAILURE RISK

McNeil is a founder of Sanderling Ventures and a founding investor in DalCor along with Canadian businessman André Desmarais. The company also received funding from Caisse de dépôt et placement du Québec, the Fonds de solidarité FTQ, CTI Life Sciences Fund, and other undisclosed investors. Since he assumed the role of DalCor's CEO, McNeil's priority has been to reduce the risk of failure for the company's first trial. The way he sees it, the dal-OUTCOMES trial worked. "It's unusual; you have a clinical trial where everything was in place, but they did not screen for the right genome."

It was only after the dal-OUTCOMES trial was terminated that one of its investigators, Jean-Claude Tardif, analyzed the data using DNA to parse the results. Tardif is director of research at the Montreal Heart Institute and designed the current trial, along with

IS DALCOR PHARMA THE NEXT UNICORN?

DalCor Pharmaceuticals is number two on a recent list highlighting Canada's 50 most financially attractive private tech companies. The Narwhal List is compiled by The Impact Centre within the University of Toronto and shows private Canadian venture-capital-backed companies with the highest Financial Velocity. Financial Velocity is the amount of funding a firm has raised divided by the number of years it has been in existence. It is expressed in millions of dollars per year. This measure reports the rate at which companies raise and consume capital. According to the list, DalCor is a contender for unicorn status, but likely would still need to raise another $50 million to reach that level.

More info at www.impactcentre.ca/narwhal

Marc Pfeffer, a cardiologist at Harvard's Brigham and Women's Hospital. Tardif's analysis showed that a single gene, ADCY9, was associated with the patient outcome. One single nucleotide polymorphism, or SNP, was chosen to help find patients in the new trial to test dalcetrapib. (In addition to the license for dalcetrapib, DalCor also has a license for the rights to the ADCY9 genetic marker.)

To prove that dalcetrapib need only be prescribed to the right patients to work as expected, McNeil has fought to keep the dal-GenE study design simple so that the results can be directly compared to the original data. "The most important decision we made was to repeat as closely as we could the dal-OUTCOMES trial, changing only the genomic configuration of the patients," he says. "We have felt strongly that we needed to change only one variable at a time. We stuck to that."

In the past year, the company has initiated over 750 clinical sites in 30 countries. Expansion has paid off, and, as of May 2017, nearly 40 percent of the patients needed had been enrolled in the study. The study is on track to complete enrollment in two years, instead of the almost three years the company had expected. The genetic component seems to stimulate interest in patients and investigators.

Throughout this stage, McNeil and his colleagues decided to keep DalCor a virtual company to keep costs down and move the development phase along more quickly. They also hired an experienced Chief Medical Officer, Donald Black, M.D., a pharmaceutical and device-industry veteran who worked for Warner-Lambert/Parke-Davis as the head of clinical development for Lipitor. Black says the market is ripe for a drug improving upon statins because "many people on statins have a subsequent heart attack."

FROM STIGMA TO STANDARD OF CARE

Despite the need to improve on statins, CETP inhibitors have a track record that is still fresh in the minds of industry leaders. "The big hurdle is that people believe this class of drugs does not work," McNeil says. Precision/personalized medicine is not new to those who develop cancer treatments. Cardiovascular researchers have a different experience. "When you say this is like Herceptin, they start to understand the potential, but are still skeptical," McNeil says. Black points out that 2 million people per year suffer acute coronary syndrome (ACS), an umbrella term that includes heart attacks as well as severe chest pain due to reduced blood flow to the heart. That number is far greater than the number of cancer patients receiving precision care, he adds.

DalCor is combatting the stigma of CETP inhibitors by highlighting existing data on dalcetrapib, as well as conducting new research aimed at describing the drug's mode of action — the kind of data the FDA likes to see anyway. "It helps people become comfortable that this is a logical, rational program," McNeil says. He points to the DNA analysis published in 2015 that also included a prospective analysis of patients who took part in the dal-PLAQUE-2 study. The original analysis showed that dalcetrapib did not positively alter atherosclerosis as measured by carotid intima-media thickness (IMT). The new DNA prospective analysis showed that AA individuals indeed showed a significant reduction in IMT when treated with dalcetrapib. In contrast, the ACS patients with GG showed a progression in coronary atherosclerosis, while AG patients showed intermediary results.

"The big hurdle is that people believe this class of drugs does not work."

ROBERT MCNEIL, PH.D.
CEO, DalCor Pharmaceuticals

Additional mode-of-action studies are underway, and DalCor's leadership is hopeful that they can build a strong case for dalcetrapib and overcome the stigma. "We think we understand the safety of dalcetrapib very well. Now, it's about getting other people to see what we see," Black says.

Prospects For Healthcare Capital Markets In 2017

JOHN NOLAN AND STEVE BROZAK

As life sciences asset managers, our evaluation of the life science capital markets for the second quarter of 2017 is one of confidence, mediated by prudent caution. Our view has been based on a confluence of subjective and objective factors.

The election of Donald Trump has raised prospects for reduced government regulations in a wide range of areas, including the possibility for a more lenient process for drug and biologic approvals and the repatriation of trillions of dollars now stranded offshore. At the same time, increasing patient dissatisfaction with their care, financial uncertainty, and uncertainty around the ability of Congress to pass meaningful legislation (healthcare or otherwise) mitigate our view. Uncertainty, however, is opportunity, and we believe this is an opportune time for healthcare investors who have the skill and insight to take advantage of the growing dispersion between "winners" and "losers" in the narrative that is unfolding.

STRANDED OFFSHORE CAPITAL

One of the drivers of upside return is the strong possibility of a large cash infusion into the capital markets, increasing the prospects for massive acquisition and investment opportunities. This would be particularly beneficial to the smaller and mid-cap biotechs, which serve as the engines of innovation and as an outsourced developmental pipeline for the larger pharma firms that eventually acquire or partner with them.

The potential large infusion of capital would come from U.S. corporate profits — estimated at ~$2.6 trillion — now stranded offshore. Corporations have been loath to repatriate these funds because the current 35 percent statutory corporate income tax would force a sacrifice of $91 billion, far too much for corporations to forego. The election of Trump, who repeatedly pledged to repatriate the offshore-held funds, increases the likelihood that those funds may come home.

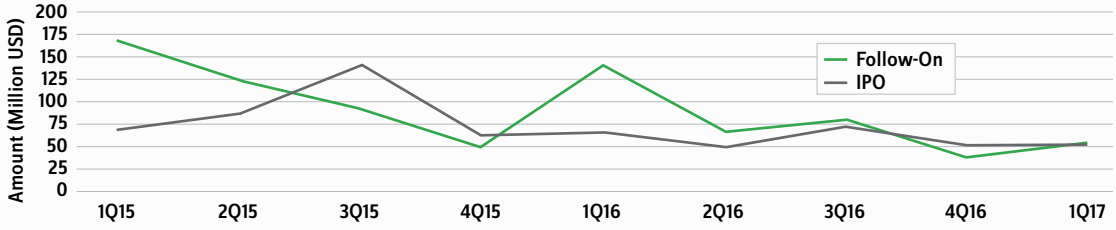
Valuations in the healthcare sector and industries like biotech are also attractive. At a little above 16 times forward earnings, the S&P 500 healthcare sector is admittedly trading at levels approximately 15 percent higher than its 10-year average; however, on a relative basis, the sector is trading at a significant discount to the overall S&P 500. Even the absolute valuation opportunity in biotech is also attractive, with the S&P Biotechnology Select index selling at a discount to its inception average of 6.1 times on a price-to-book basis and down almost 25 percent from its valuation highs of 2014 through 2015.

A RALLY IN THE MARKETS

We believe these factors have, in part, precipitated the turnaround in the healthcare and biotech financial markets. During 2016, healthcare was the worst performing sector in the S&P 500, returning approximately -2.7 percent, despite the late-year Trump rally. In the first quarter of 2017, that trend has clearly reversed. The S&P 500 healthcare sector finished the first quarter of 2017 with a total return of approximately 8.4 percent. Biotechnology has fared even better. After losing more than 16 percent last year, the S&P Biotechnology Select index returned over 17 percent in the first quarter.

Much of the rally in biotech and healthcare, however, has been fueled by the belief that the Trump administration will be less likely to push through substantial legislation curtailing pharma prices. Additionally, we believe that current market valuations assume the administration and Republican-controlled Congress will facilitate a probusiness agenda by enacting corporate tax reform and potentially reducing the regulatory burden for drug approval.

AVERAGE FOLLOW-ON AND IPO AMOUNTS FOR TRANSACTIONS PRICED IN CALENDAR QUARTER



SOURCE: Thomson Reuters Eikon

The cautiousness in our confidence arises from the mitigation of positive trends by several negative occurrences. President Trump called out the pharma industry on high drug prices on January 11 and March 7, which resulted in a -3.5 percent and -1.7 percent pullback in the S&P Biotechnology Select index. The failure of the House to take a vote on the first iteration of the American Healthcare Act (AHCA) and the immediate objections to the subsequently passed version could portend an inability of the administration and Congress to pass any sweeping legislation. Corporate tax reform, much like healthcare reform, may not come so easily or as expeditiously as the market may expect. With such impediments, there is a very real risk that the current rally could lose and potentially reverse momentum by the end of the summer.

THE EFFECT OF THE AHCA

Even if the AHCA becomes law in its present form, it could have a significant effect on the pharma and biotech markets. In a *Forbes* commentary, we observed that while the proposed legislation did not specifically address drug manufacturers, many of the largest biotech firms would be directly impacted through changes the law would impose on the Medicaid system, causing a loss of up to 15 million beneficiaries by 2026 and billions of dollars less revenue for several biotech and pharma companies.

In 2015, CMS reported that Medicaid spent approximately $57 billion on prescription drugs for more than 73 million beneficiaries, with the majority (65 percent) of spending directed toward 155 drug products. While these sales figures do not include rebates for net spending, we do know that from 2014 data that Medicaid spent approximately $42 billion on prescription drugs and received $20 billion in rebates from manufacturers, for a net drug spend totaling $22 billion. While it is not clear how new iterations of the AHCA will take shape regarding its impact on Medicaid enrollment, we are cognizant of the risk that this may pose to the biotech industry.

Healthcare equity transactions also have been more challenging during the last few quarters, both through follow-on offerings and IPOs. The number of deals has marginally dipped lower, and the amount per transaction has steadily declined. This could suggest a change in investor risk appetite for healthcare offerings or possibly, changes in the quality of the offerings themselves.

The pace of M&A for biotech companies also has been slower than expected despite the attractive valuations noted previously. Pharma and biotech acquisitions totaled $44 billion in the first quarter of 2017, down 13 percent from a year earlier, and 35 percent below the first quarter of 2015, according to Bloomberg. However, cash on hand for large-cap U.S. pharma firms remains close to all-time highs (>$105 billion), while overall leverage, though increasing, still remains at moderately low levels. We do not believe that the diminished M&A environment is the result of a lack of innovation; 12 drugs received approval by the FDA in the first quarter, which is >50 percent of the number of approvals for all of last year and on pace to approach the 45 approved in 2015. Instead, many companies may be waiting for legislation to repatriate their overseas cash, which could unlock a wave of activity.

All told, we remain cautiously confident for the remainder of 2017, despite the potential obstacles and uncertainties, because we believe the impact of legislation, rising interest rates, and lower transactional volumes are somewhat counterbalanced by the continued demographic tailwinds and attractive valuations in biotech and healthcare. Plus, we see the potential for upside optionality attributable to tax reform that could lead to cash repatriation and an environment that is more conducive to M&A activity.

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The Power Of Small Wins

And How To Keep Them Going

TERESA AMABILE

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Consider two facts. One: Many senior scientists and engineers in biopharma, during careers of 20, 30, even 40 years, have never been directly involved in developing a commercially successful drug. Not once. Two: Of all the things that can keep people engaged and productive in meaningful creative work — like discovering groundbreaking disease treatments — the single most important is simply making progress. Because drug R&D is likely to remain difficult even as technology advances, the challenge for you, as a leader, is this: How do you maintain the motivation of talented researchers, young and old, when progress is slow?

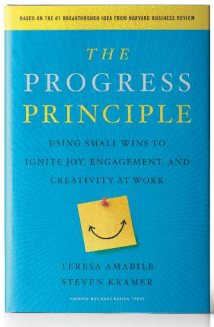
By analyzing nearly 12,000 diary entries from 238 people doing the most important innovation projects in their companies, my team and I discovered that people are most creative when they are deeply engaged in their work and experiencing positive emotions. In fact, people are 50 percent more likely to come up with a new idea or solve a problem creatively on days of positive mood than days of negative mood. Setbacks in the work, the opposite of progress, are the main culprits in precipitating such negative mood. The bad news is that the negative effects of setbacks are three to four times stronger than the positive effects of progress.

CREATING MOMENTUM WITH SMALL WINS

The good news is that even incremental progress in meaningful work can powerfully boost engagement and elevate mood. We call that *the power of small wins*: fully 28 percent of seemingly trivial events at work have an outsize impact on motivation and emotion. Here's how to harness that power in the difficult business of biopharma invention:

1. Aspirational ultimate goals: Inspire your discovery teams with lofty, powerful goals in each project, tying those goals to a meaningful purpose.
2. Chunk the ultimate goal into intermediate steps: Because it can take years to achieve that ultimate goal, reaching more manageable goals along the way — even minor ones — can keep people creatively engaged. Those small wins generate momentum.
3. Create psychological safety: Maintain a day-to-day work environment where people welcome ideas, even seemingly crazy ones, and feel safe calling out failures and mistakes because they know debriefs will focus on the work — and not scapegoat the people involved.
4. Celebrate progress and "smart setbacks": Take a moment to recognize even small steps forward and — this is incredibly powerful — even recognize failures, when the effort was a good one.
5. Extract failure value: Even failed projects usually yield new knowledge and products — like an interesting new molecule — that can be repurposed later. Be sure that knowledge extraction happens, and that the people involved in the original project know about it.
6. Keep researchers in "the discovery chain": Often, scientists who work on drug discovery in early stages have no idea what happens to their efforts as the project morphs and travels toward commercialization. Keep people informed, with an internal "genealogy" of each project so that no one, after 40 years, will say they've not been associated with a successful drug.

Taking these steps will maximize the likelihood that your scientists will bring their most creative selves to every project, every time. L



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