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JANUARY 2016

Balancing The Business Of Corporate Social Responsibility

p. 18

JULIE GERBERDING, M.D.
EVP of Strategic Communications, Global Public Policy, Population Health, Merck

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Do What Is **Right**

ROB WRIGHT Chief Editor

I once had the opportunity to see Norman Schwarzkopf speak in person. It was a powerful experience, occurring shortly after the four-star general had retired from the United States Army. Having successfully led Operation Desert Storm, the U.S. military effort to liberate Kuwait following an invasion by Iraq in 1990, Schwarzkopf detailed the dilemma leaders often face — doing what is right. The late general was of the opinion that people always know the right thing to do; the hard part was actually doing it. Schwarzkopf said, "Do what is right, not what you think the high headquarters wants or what you think will make you look good." A very accomplished leader, his principle sounds as if it would be so easy to follow. Yet every day we see countless examples of supposed leaders failing to follow that which seems most basic. Consider the recent case of Volkswagen (VW), the automaker that deliberately set out to design a means to circumvent emissions control standards.

Dating back to 2009, VW installed a "defeat device" on nearly 500,000 vehicles, allowing them to successfully cheat U.S. emissions tests. The strategy was known at the highest levels within the company and provided VW with a significant, albeit unfair, advantage over its competitors trying to play by the rules and regulations. VW's rejection of ethical engineering standards most likely played a major role in vaulting the company past Toyota as the world's largest automaker this past summer.

One day after acknowledging the emissions test scandal at VW, CEO Martin Winterkorn announced he was resigning. "I am shocked by the events of the past few days," the executive said in a released statement. "Above all, I am stunned that misconduct on such a scale was possible in the Volkswagen Group." Although the former CEO accepted responsibility for the scandal, he did so asserting that he was "not aware of any wrongdoing on my part." From my perspective, Winterkorn should have heeded some of Schwarzkopf's other advice: "When placed in command, take charge." In other words, don't pass the buck.

In our industry, this concept of "doing what is right" in business was the crux of a recent controversial issue involving BIO and Turing Pharmaceuticals.

Shortly after Turing acquired Daraprim, a treatment for toxoplasmosis, with the full support of its CEO, Martin Shkreli, the company increased the price of the drug by more than 5,000 percent! While the move resulted in a media firestorm causing the company to quickly backpedal, one organization and one leader did not. In an unprecedented move, BIO, the world's largest biotech trade association, kicked Turing out and returned the company's membership dues. The move was spearheaded by BIO chairman, Ron Cohen, and the BIO executive committee. And, as you may expect, some in today's mainstream media took issue with BIO's application of Schwarzkopf's principles, implying that these actions were a mere "tossing of Turing under the proverbial bus." In other words, not only the decision by BIO to do the right thing, but actually do it, just wasn't good enough.

When it comes to the proper practice of corporate social responsibility in our industry, does it feel to you that no matter how hard we try, we please very few of the people, very little of the time? If so, don't you think it is time we do the right thing, and start doing something about it? L

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LIFE SCIENCE LEADER
5340 Fryling Rd., Suite 300 / Erie, PA 16510-4672
Telephone: 814 897 7700 / Fax: 814 899 4648
WWW.LIFESCIENCELEADER.COM

SVP OF PUBLISHING/PRODUCT DEVELOPMENT
Jon Howland / Ext. 203
jon.howland@lifescienceconnect.com

VP OF CONTENT
Ed Hess
ed.hess@lifescienceconnect.com

EDITORIAL DIRECTOR
Dan Schell / Ext. 284
dan.schell@lifescienceleader.com

CHIEF EDITOR
Rob Wright / Ext. 140
rob.wright@lifescienceconnect.com

EXECUTIVE EDITORS
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

Louis Garguilo
louis.garguilo@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Trisha Gladd
trisha.gladd@lifescienceconnect.com

SENIOR DIRECTOR OF PUBLISHING
Perry Rearick
perry.rearick@lifescienceconnect.com

VP OF AUDIENCE DEVELOPMENT
Michael Bennett
michael.bennett@lifescienceconnect.com

PRODUCT DIRECTOR
Jenell Skemp
jenell.skemp@lifescienceconnect.com

PROJECT MANAGER
Megan Rainbow
megan.rainbow@lifescienceconnect.com

DIRECTOR, LIFE SCIENCE TRAINING INSTITUTE
Bill Beyer
bill.beyer@lifescienceconnect.com

PUBLISHER, CLINICAL & CONTRACT RESEARCH
Sean Hoffman / 724 940 7557 / Ext. 165
sean.hoffman@lifescienceconnect.com

PUBLISHER/BIOPHARM & LAB
Shannon Primavere / Ext. 279
shannon.primavere@lifescienceconnect.com

PUBLISHER/OUTSOURCING
Cory Coleman / Ext. 108
cory.coleman@lifescienceconnect.com

ENGAGEMENT MANAGER
Kevin Morey
kevin.morey@lifescienceconnect.com

GROUP PUBLISHER/OUTSOURCING
Ray Sherman / Ext. 335
ray.sherman@lifescienceconnect.com

BUSINESS DEVELOPMENT MANAGER
Mike Barbalaci / Ext. 218
mike.barbalaci@lifescienceconnect.com

SR. ACCOUNT EXECUTIVE
Scott Moren / Ext. 118
scott.moren@lifescienceconnect.com

PRODUCTION DIRECTOR
Lynn Netkowicz / Ext. 205
lynn.netkowicz@jamesonpublishing.com

MANAGE SUBSCRIPTIONS
814 897 9000 / Ext. 315
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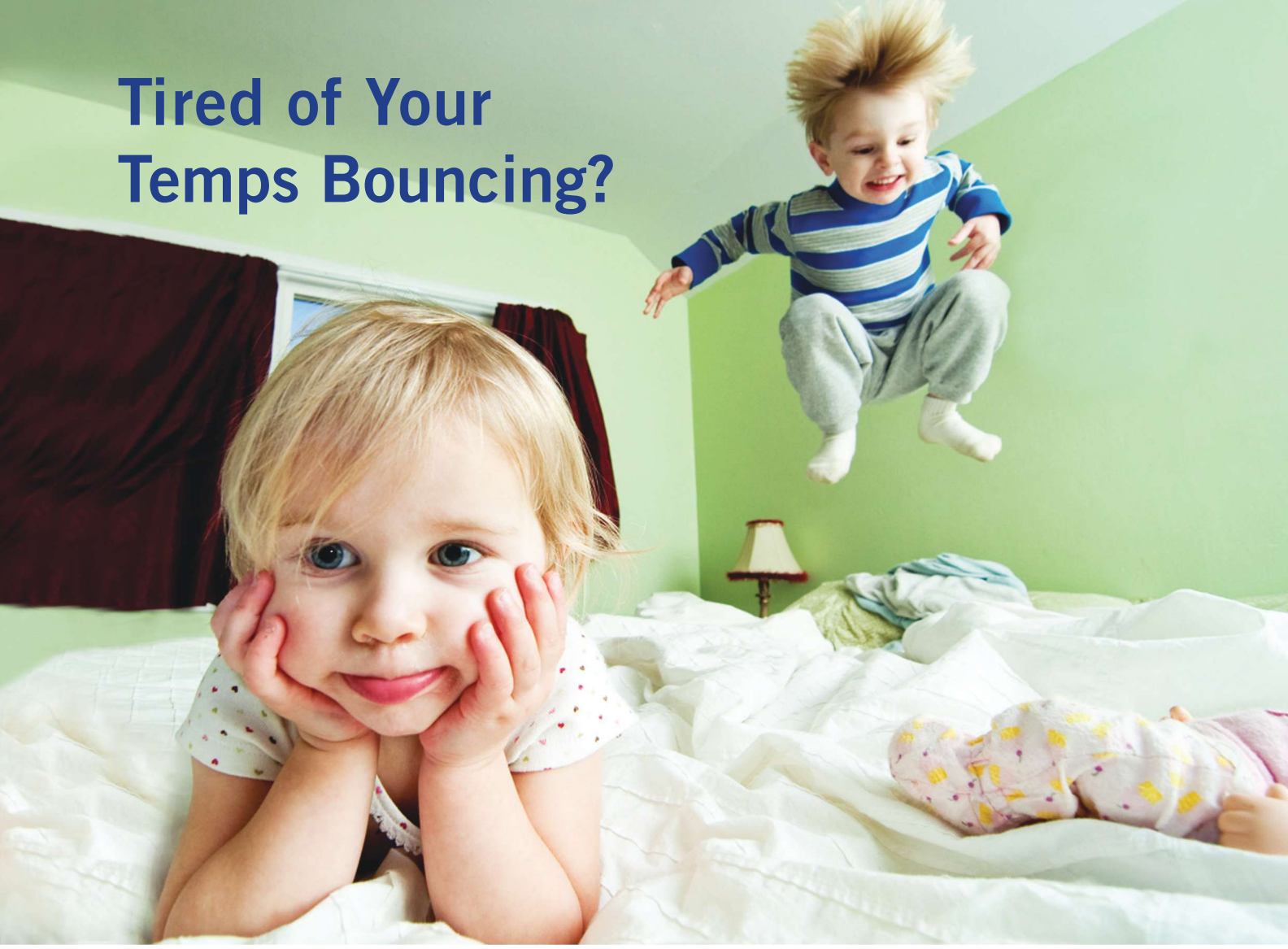

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Q How should a mentee go about selecting a mentor?

A A MENTOR, BY DEFINITION, is one who is disinterested in your success. That means your success does not reflect directly on the mentor. Such a definition may be too narrow for many organizations, but it is something to consider as you select a mentor. Look for one who has a track record of working with others, and talk to them about the influence they had on the lives of those they mentored. Most importantly, select a mentor who complements you. My advice is to look for someone who can teach you what you don't know. This individual may be in your field but has experience and wisdom far beyond your own. A mentor must be one who is willing to listen but not always someone who tells you what you want to hear. You want a mentor to challenge your assumptions and open new avenues of exploration.

JOHN BALDONI
is chair of the leadership development practice of N2growth, a global leadership consultancy. John is the author of more than a dozen books, including the recent *MOXIE: The Secret to Bold and Gutsy Leadership*.

Q From an investor perspective, what are the big trends for 2016?

A AFTER A HALF-DECADE OF OUTPERFORMANCE, 2016 will shape up to be a "show-me" year. On the cancer front, especially immuno-oncology, we will find out whether the exciting early clinical results will result in longer, more durable responses. We will also learn whether these new agents will be effective when used in combination with other drugs. In the gene therapy and gene editing space, we will see whether the long-anticipated effectiveness of these technologies begins to be proven in the clinic. On the Big Data front, we will see how traditional technology companies begin to leave their footprints in life sciences. On the M&A front, we will see whether the large pharma companies' strategy of acquiring small-to-midsize biotech companies will continue. Lastly, on the reimbursement front, we will see more innovative deals being developed between biotech companies and insurers.

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

Q What are some of the most impactful leadership books you've read during your career?

A THESE ARE "MUST READS" FOR MY MENTEES. I keep several copies handy for people in need because they are too valuable to return.

1. *QbQ! - The Question Behind the Question* by John G. Miller has great lessons in personal accountability (e.g., the only person you can change is you).
2. *The 7 Habits of Highly Effective People* by Stephen R. Covey provides foundational and timeless teachings for interacting with others for greater impact and continuous personal improvement.
3. *12: The Elements of Great Managing* by Rodd Wagner and James K. Harter gives insight on providing the basic and extra needs of your employees to deliver engagement and greater impact.
4. *Leading Change* by John P. Kotter is a road map for leading your organization through change. Wish I had read this much earlier in my career.
5. *The Speed of Trust* by Stephen M. R. Covey explains the foundations for building trust for extraordinary outcomes.

JAMES ROBINSON
James Robinson is the former VP for vaccine and biologics technical operations for Merck & Co. In this role, he supported the manufacturing strategy, process development, technical transfer, approval, and production of Merck's vaccines and biologicals at eight internal sites in the U.S. and Europe and several partner sites globally.

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Reemerging with a licensed drug for a rare neuromuscular disease – and treading carefully to set its price

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Catalyst Pharmaceuticals is developing drugs in the neuromuscular disease area, with Firdapse (amifampridine phosphate) as its lead candidate. Firdapse treats Lambert-Eaton Myasthenic Syndrome (LEMS), a rare condition in which the immune system attacks calcium channels in neuronal junctions, causing muscle weakness. Firdapse is a potassium-channel blocker that counters that condition by increasing calcium-channel flow. Catalyst is also developing CPP-115, a GABA-aminotransferase inhibitor, for the treatment of infantile spasms and Tourette's disorder.

WHAT'S AT STAKE

This month, I depart from one of the chief criteria for Companies to Watch — the subject company will have had little or no press coverage to date — but, I believe, with good reason. As reported extensively in the July 19, 2015, *Miami Herald*, Catalyst epitomizes what so many companies now face with new, possibly breakthrough or essential drugs they in-license or acquire the rights to develop: Do they price them at a premium and risk limited patient access (and a public uproar), or price them as low as possible to ensure maximum access? I spoke with Catalyst President and CEO Pat McEnany and CSO Steven Miller about the unique factors each company in that situation must consider before making a pricing decision.

Examples for comparison: Gilead did buy its Hep C blockbusters but took on a great deal of risk and expense to develop and market them. Turing merely bought an essential but inexpensive drug for a tiny market and promptly inflated the price by several orders of magnitude. Catalyst has an approach closer to Gilead's — taking on the risk of developing a drug not approved in the United States for any indication, while carefully contemplating the price should the drug gain FDA approval as hoped in 2016.

After Catalyst's initial lead candidate, a drug for cocaine and methamphetamine addiction, washed out of clinical trials in 2012, the company happened upon the opportunity to acquire the U.S. rights to Firdapse, for treating LEMS and congenital myasthenic syndromes (CMS), from BioMarin, which was already marketing the product in Europe. But that did not ensure a painless transition; the FDA required Catalyst and BioMarin to conduct 57 nonclinical studies and six clinical studies, including a Phase 3 trial, and requested that Catalyst file a rolling submission of the NDA (new drug application).

Compound pharmacies have made the basic drug, 3, 4 diaminopyridine (3, 4 DAP), available to patients at relatively low cost but in a free-base (possibly less stable and soluble) formulation, and perhaps with uncertain supply and quality. But the company has tested the waters with its LEMS constituents — patients, physicians, and payers — at medical meetings such as the AANEM (American Association of Neuromuscular Electrodiagnostic Medicine) meeting and in discussions with patient associations, including NORD (National Organization for Rare Disorders). McEnany describes some of the feedback:

"There were about 150 neuromuscular physicians who attended our sponsored industry forum at AANEM, and they found it to be very well-prepared and informative regarding LEMS and CMS. Our research with payers and physicians is ongoing. We have had an opportunity to pressure-test several price points without any significant pushback from payers." At NORD, he says, the company met with LEMS patients and KOLs, a rare gathering for a rare disease. "Interestingly, all of the patients we met were initially misdiagnosed."

Does McEnany agree that companies making pricing decisions for rare disease or specialty drugs face a trade-off between profits and patient access? "I don't believe a drug's price limits access as long as value for that treatment can be demonstrated," he answers. "This is particularly true for orphan diseases such as LEMS. Our goal has always been to make sure *all* patients with LEMS and CMS have access to Firdapse."

How will we know, if and when Catalyst sets a price for Firdapse, that it matches those criteria? This is one company we will have to watch.

PAT McENANY
President and CEO

Vital Statistics

18
Employees

Headquarters
Coral Gables, FL

Finances

$122,552,113

VC (or private rounds)
$5,067,113

IPO
$17,638,000

Other public financings
$99,847,000

Lead institutional investors: BioMarin, Baker Bros., Consonance Capital, Federated Global, Broadfin Capital, Franklin Advisers

Research partnership funding

Previously, National Institute on Drug Abuse - $10M for cocaine addiction trials

Other partners

BioMarin invested, owns 8.05% in Catalyst from its sale of North American license for Firdapse to treat Lambert-Eaton Myasthenic Syndrome

Acquired worldwide license for CPP-115 from Northwestern University.

Latest Updates

December 2015
Completed FDA NDA filing for Firdapse

Initiated proof-of-concept clinical trial of Firdapse in patients with anti-MuSK antibody myasthenia gravis

Data from safety/tolerability study for CPP-115

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Enactment Of Site-of-Service Neutrality Could Open Door For 340B Reform

JOHN McMANUS The McManus Group

I have written a lot about the ill effects provider consolidation has on competition and patient choice. But Congress made an interesting move recently when it enacted the Bipartisan Budget Act of 2015 in November. It made hospital acquisition of physician practices and competing ambulatory surgery centers (ASCs) less financially appealing. And in doing so, Congress illuminated a possible path to reform 340B, the pharmaceutical pricing scheme for certain nonprofit hospitals that has ballooned in recent years.

For several years, the Medicare Payment Advisory Commission (MedPAC) and the Health and Human Services Office of Inspector General (OIG) have opined that hospitals should not receive inflated payments from Medicare for physician and outpatient surgical services that are paid a fraction of the amount to independent physician practices and ambulatory surgery centers in the community.

- MedPAC found that over the past seven years outpatient services increased by 33 percent in hospitals, and this "growth, in part, reflects hospitals purchasing free-standing physician practices and converting them into hospital outpatient departments [HOPDs]."
- MedPAC also documented substantial shifts in market share in high-cost cardiology services from the physician office setting to hospitals — driving costs higher for patients and the program because of the higher reimbursement levels at hospitals for the identical services.
- MedPAC recommended cutting hospital payments for evaluation and management codes to the physician office level, which would save the program more than $10 billion over the next decade.

Meanwhile, the OIG recommended reducing hospital payments for low-risk, outpatient surgical services commonly performed at ASCs to the ASC rate, which it estimates would save Medicare $15 billion over five years and beneficiaries another $2 billion to $3 billion in lower copayments. As a result, payments for a colonoscopy would drop from about $1,400 to $630, and cataract surgeries would fall from $1,745 to the ASC rate of $976. OIG concluded that it was irrational to pay almost twice the amount for a procedure commonly performed in the community setting at the most expensive site of care.

But, until November's budget bill, the powerful hospital lobby had successfully swatted away such proposals, arguing that those swollen fees were necessary to ensure patient access. Thomas Nickels, executive VP of government relations and public policy for the American Hospital Association (AHA), commented that a site neutrality policy "may endanger patient access to care, especially among patients who are sicker, the poor, minorities, and seniors who often receive care in hospital outpatient departments."

Wait — access to care for vulnerable populations would be endangered because patients received that care at an independent physician practice or at a hospital-acquired practice that will be paid at physician office rates? Why is that? They don't say.

But rather than take the AHA head-on, Congress enacted a provision that *prospectively* limits reimbursements of services to the physician office or ASC level for *future* hospital acquisitions. In essence, the policy permits hospitals to keep what they have but arrests future windfalls. Under the policy, hospitals can continue to acquire physician practices and outpatient surgery centers, but can no longer reap the excessive payment rates when those community providers (often located miles away) are absorbed by hospitals. The Congressional Budget Office scored the provision as saving $7.9 billion over 10 years — that is a lot of forgone windfalls!

This policy alone, of course, will not halt hospital acquisitions of physician practices. Those acquisitions may continue for reasons related to increased market power and the capture of referrals for ancillary services, but at least Medicare's role in fueling those acquisitions will be terminated.

The policy should help slow the growth of the 340B program. A recent Moran Company study commissioned by The U.S. Oncology Network found that Medicare pays about twice as much to hospitals than to freestanding oncology practices for the identical chemotherapy administration. (See attached table showing Medicare reimbursement to an actual physician practice and what that reimbursement would have been to a hospital for the identical services.)

It is no wonder that hospitals are acquiring oncology and other physician practices at such a rapid pace. According to a 2014 Berkeley Research Group report, 340B DSH (disproportionate share hospital) hospital acquisitions of community oncology practices increased more than eightfold from 2004 to 2011. The Moran Company found hospital outpatient market share of chemotherapy administration skyrocketed from 13.5 percent in 2005 to 33 percent in 2011. (More recent statistics are not available, but that escalation continues unabated.)

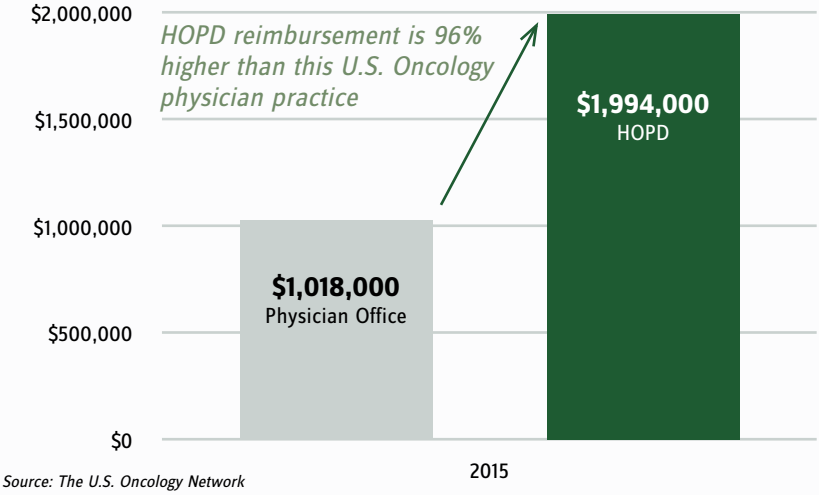
Of course, hospital acquisition of physician practices is only one reason for the growth of the 340B program. Between 2003 and 2013, the volume of 340B revenue nearly tripled to $7.5 billion. From 2005 to 2010, the number of hospitals in the 340B program grew 134 percent from 583 to 1,365 and from 2010 to 2014 grew another 57 percent to 2,140 covered entities. At the same time, the number of 340B entities contracting with retail pharmacies has soared to more than 3,000 this year from just 1,000 in 2010.

For the past several years, the pharmaceutical industry has been focused on fundamental reform of the 340B program — narrowing the definition of the patient to uninsured or indigent individuals, prohibiting contracting with multiple off-site pharmacies, limiting 340B revenue for prescriptions to Medicare beneficiaries, among other reforms. But those efforts have run into a brick wall — the powerful hospital lobby with active constituents in every member's district. In addition, the political environment has become more toxic for the pharmaceutical industry, with increased scrutiny of pharmaceutical pricing.

So perhaps a new strategy based on the recently enacted site-of-services reform may be worthy of contemplating? Apply a moratorium to arrest further 340B growth until Congress can develop consensus on a more fundamental reform. Such an approach could entail any or all of the following elements:

HOPD Reimbursement for Cancer Rx Administration is Almost Double Physician Office Reimbursement

The graph below shows actual reimbursement for one medical oncology practice compared to the HOPD reimbursement rate for the identical chemotherapy administration service.



Source: The U.S. Oncology Network

- Prohibit the addition of any new 340B DSH hospitals.
- Prospectively prohibit physician practices acquired by 340B hospitals from accessing 340B prices (consistent with definitions in the Bipartisan Budget Act).
- Prohibit the addition of any "child sites" of existing 340B DSH hospitals.
- Prohibit addition of any off-site pharmacy (including mail-order) of any 340B DSH hospital.

Of course, pharmaceutical industry consensus is needed on any proposal — whether fundamental reform or more modest steps such as transparency of how hospitals are using 340B revenue or a moratorium — as legislators are unlikely to engage on a solution that cannot find broad support. A strong policy case can be made for fundamental reform of the 340B program, particularly in the wake of the draft guidance issued by HRSA (Health Resources and Services Administration) in August which validated the need for greater oversight and control of the 340B covered hospitals. But healthcare policy is often made by crosswalking a successful approach in one sector to a different sector.

The new year provides an opportunity to float new ideas and approaches. Inaction is no longer a viable option. L

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

Can You Afford To Take Biopharma Innovation For Granted?

ALLAN L. SHAW @ALLAN_L_SHAW

Notwithstanding biopharma's immeasurable contribution to society and the promise of delivering many more exciting medicines, the industry remains the favorite whipping boy due primarily to drug pricing. Biopharma continues to serve as the proverbial lightning rod of criticism by politicians, payers, doctors, and patient-consumers, which is ironic given that such fervent disdain and criticism is usually reserved for the industries causing global health problems, such as tobacco, not the industry solving them. As part of this debate, perhaps myopically, there has been a great deal of focus and scrutiny (myself included) concerning the inequity in U.S. drug prices relative to the rest of the world. However, when considered on a macro level, why should the U.S. subsidization of global medicine be any different from other U.S. global leadership roles (underwritten by U.S. taxpayers)?

Arguably speaking, the U.S. drug price premium relative to the rest of the world is simply another form of U.S. aid (e.g., foreign, defense, humanitarian, international organizations such as the United Nations and NATO) that provides much greater benefits to mankind. Unfortunately, the funding mechanism is regressive in nature and much more akin to a sales tax, inevitably placing undue burden on patients and becoming an impediment to optimal healthcare. This dynamic is the heart of a much more fundamental and overarching question: How do you facilitate optimal cost-effective patient access to innovative medicines while providing the necessary financial rewards/incentives to keep the prolific scientific engines running? Particularly, global cost-containment initiatives and the resulting price controls in the rest of the world have put pressure on achieving profitability in the U.S.

While some politicians such as Bernie Sanders may be campaigning that "the pharmaceutical industry has become a health hazard for the American people," nothing could be further from the truth. There is no denying it — innovative medicines have and will continue to have a profound role in saving lives and impacting the quality of life for millions, not just in America, but around the world. With ongoing advancements in understanding the underlying basis of physiology and disease, we are only just beginning to see the tip of the iceberg, and the outlook has never been brighter. In parallel, U.S. drug prices have already started to succumb to gravitational forces from fundamental reform in the U.S. healthcare ecosystem. The consolidation of pharmacy benefit managers (PBMs) and their increasing purchasing power and the evolving value-based reimbursement system are changing the commercial landscape. This new reality should reward truly innovative medicines while facilitating the extinction of "me-too" branded products. With that said, if European-style price controls were enacted in the U.S., what would happen to the pace and capacity of translating scientific insight into products that deeply impact public health?

The innovation that leads to effective treatments for diseases that affect public health depends upon a complex and thriving ecosystem that involves basic research in universities and research institutes, drug discovery and development (R&D) in the biopharmaceutical industry, and clinical research in hospitals. R&D is risky and costly; therefore, high financial returns are necessary to induce investment in researching and developing new treatment modalities. So yes, it is easy to characterize U.S. drug costs as "price gouging," but most of the time, that kind of blanket description severely underestimates all the time, effort, money, and risk that

"How do you facilitate optimal cost-effective patient access to innovative medicines while providing the necessary financial rewards/incentives to keep the prolific scientific engines running?"

went into developing a pill, injection, or technology. Changes in federal policy that affect the returns of biopharma R&D may have dramatic effects on the investment patterns of the industry. Given this sensitivity to the policy changes, it is important to consider the unintended consequences of the effects on R&D, similar to pulling on a loose string on a sweater. The risk/reward model is the ultimate arbiter in resource allocation (e.g., human and capital). The power of this alignment is best illustrated by the proliferation of drugs targeting orphan diseases, which currently make up approximately 13 percent of global branded Rx sales, a percentage that is growing at almost twice the market rate. It should not be surprising that the favorable risk-adjusted return on such products is driving further R&D investments in orphan diseases.

WHY THE U.S. IS THE EPICENTER OF BIOPHARMA INNOVATION

In my view, it is hardly a coincidence that the U.S. is the epicenter of biopharma R&D innovation. It is all about the U.S. ecosystem, which is second to none with its deep concentration of academics, companies, talent, and capital. These characteristics and their interconnection are fundamental drivers that enable the ecosystem's capacity to incubate cutting-edge science and create and capitalize companies. In contrast, it is extremely challenging to do likewise abroad, as other parts of the world do not possess the critical mass of resources or investor sophistication (e.g., lack of early-stage capital to fund innovation, smaller pools of talent, a lack of entrepreneurial bench strength). Inevitably, great science remains untapped, and many early-stage players are starved for investment due to deficiencies in their ecosystem. To put this in better perspective, the $450-million round closed by Moderna Therapeutics, a U.S.-based venture-backed company pioneering the development of messenger RNA (mRNA) Therapeutics, was more than all of the VC money invested in the U.K in 2014. In the two-and-a-half years since emerging from stealth mode, Moderna has raised $600 million, 25 percent of what the U.K. biotech industry managed over the past decade. Consequently, this dynamic has contributed to the ever-increasing U.S. migration of foreign biopharmas to access its capital markets and deep pockets of resources to better facilitate growth.

The focus of all stakeholders should be centered on two goals:

- Establishing a policy framework that incents innovation rather than rewards yesterday's advances. All available tools should be considered and included, such as vouchers for priority regulatory review, exclusivity periods, and targeted tax credits. Perhaps even consider a tax amnesty to encourage the repatriation of profits trapped off-shore if they are reinvested in R&D (alleviating the need for tax inversions).
- Enabling optimal patient access to cost-effective innovative medicines. The regressive elements of patients' higher out-of-pocket costs could be partially mitigated by various forms of rebates and co-pay assistance, including coupons and vouchers for lower-income beneficiaries.

The continued increase in life expectancies should not be taken for granted. It is not an entitlement. Without the appropriate risk/reward incentives, it will be increasingly difficult, if not impossible, to continue the prolific pace of scientific advancement, particularly if the U.S. discontinues its implicit subsidiary of global medicine. It's always costlier to lead the pack, but the benefits gained from both an economic and humanitarian perspective far outweigh the costs. While one can debate the means to the end, it is important to note that "the end" includes the creation of a very exciting and pioneering scientific machine that addresses unmet medical needs and improves the standard of care for many people globally. Changes to the biopharma risk/reward model should not be done in isolation. Without good health, does anything else really matter? Be careful what you wish for.

ALLAN L. SHAW is a senior biopharmaceutical executive/CFO. He is currently a member of the board of directors for Akari Therapeutics (chairman of the audit committee) and VIVUS (chairman of the compensation committee). He was recently managing director – life science practice leader for Alvarez & Marsal's Healthcare Industry Group and formerly CFO of Serono. He has more than 20 years of corporate governance and executive/financial management experience and is responsible for more than $4 billion of public and private financings (including an IPO) and numerous business development transactions.

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How Merck Balances The Business Of CORPORATE SOCIAL RESPONSIBILITY

ROB WRIGHT Chief Editor @RFWrightLSL

When I first connected with Merck's Julie Gerberding, M.D., MPH, the original idea was to dig into the story behind the work being done on the development of an Ebola vaccine. When panic over a possible U.S. outbreak began to bubble in the fall of 2014, people questioned why an Ebola vaccine did not yet exist. While some fingered NIH budget cuts as the culprit, others, yet once again, took aim at the biopharmaceutical industry and the economics of drug development. After all, why would biopharmaceutical companies pour millions of R&D dollars into curing a disease that sporadically surfaces in low-income areas of the world where there is little or no money to be made? A year and a half later, when Merck and NewLink Genetics began reporting very positive results on their Ebola vaccine initiative, the question then turned to, "Yeah, but will it make any money?" It seemed Merck was in the rather precarious position of "Damned if you do, and damned if you don't."

But Gerberding, Merck's EVP of strategic communications, global public policy, and population health and a former director of the CDC, is savvy. During our initial conversation, she pointed out how Merck has been in such positions before. For example, when William Campbell, Ph.D. (a retired Merck research scientist) wanted to develop Mectizan (ivermectin), a treatment for river blindness in Africa, Latin America, and Yemen, despite the product having zero commercial viability, Merck supported his efforts. "We have an 'in perpetuity' commitment to make that drug available as long as it's helpful and useful on a global basis for river blindness," she adds. "In my view, we have a similar commitment to the development of an Ebola vaccine." Gerberding believes that when a company has the knowledge and expertise to impact important health problems, there is a responsibility to act, even if there is no way to create a commercially viable enterprise. It's part of the company's commitment to corporate social responsibility (CSR). And while a humanitarian impulse is the real driver of most drug development, Gerberding realizes that there has to be some form of business justification, too. "Simply putting things into the philanthropic bucket is rarely sustainable," she attests. The challenge, of course, is to figure out how to solve key health problems, such as river blindness and Ebola, in an affordable and sustainable way. Gerberding says the solution sometimes resides not just in the application of CSR initiatives, but also in finding common ground for what both business and society value.

Balancing The CSR Business Equation

The concept of CSR has been around for more than 50 years, but Gerberding says its definition has evolved into somewhat of an all-encompassing term. "Companies use CSR to describe the combination of their environmental sustainability, philanthropy, and reputation enhancement activities," she shares. "It's how they try to bring value back to the communities and people they serve." Merck, however, looks at CSR as a commitment to developing creative and innovative solutions to global health challenges, while at the same time building its business in a sustainable way.

While philanthropy is an important demonstration of Merck being a solid corporate citizen, it is also reflected in the company's approach to other CSR initiatives. For example, one of the biggest social health problems Gerberding saw countries and governments struggling with was how to achieve the millennium development goal (MDG) around maternal mortality. Referred to as MDG5, the maternal health initiative had two primary targets: between 1990 and 2015, reduce by three-quarters the maternal mortality ratio, and by 2015, achieve universal access to reproductive health. To assist in helping to achieve MDG5, Merck launched its Merck for Mothers program, a $500 million investment being made over 10 years. "With this initiative, we are trying to do something a little different than the usual CSR portfolio," Gerberding states. For Merck, the process began by meeting with country health ministers and government leaders, among others, to determine what a pharmaceutical company could uniquely do that would help the problem. "There are certain things we know how to do well [e.g., develop drugs, influence providers,

encourage patient compliance]," she explains. "But we also know how to manage supply chains and collect and analyze data." One of the components Merck is working on through the Merck for Mothers initiative is the development of a heat-stable drug that stops severe bleeding (postpartum hemorrhage) during delivery, a major cause of death for women around the world. Merck is working in partnership with Ferring Pharmaceuticals and the WHO, and the WHO recently started a clinical trial for a heat-stable version of a drug already used successfully to stop hemorrhage. "While not a commercially viable program from a profit standpoint, this program allows us to leverage some of our core capabilities, strengthen business partnerships, and hopefully provide a practical solution in areas where people don't have anything else to turn to for a solution."

Another Merck for Mothers initiative geared toward increasing access to family planning focused on the business of logistics. "There are all kinds of inexpensive contraceptives available to women, but unfortunately, in most countries the supply chain simply doesn't work," Gerberding attests. For example, in Senegal it is a struggle for clinics to maintain the cash flow necessary to buy contraceptives for distribution. Prior to the Merck for Mothers program, these clinics were out-of-stock of contraceptives 85 percent of the time. This means that when a woman showed up to get the contraceptive she needed, nearly nine times out of 10, she left empty-handed. "Working in partnership with the Senegal government, the Gates Foundation, and a couple of private-sector partners, we were able to create a completely different supply chain distribution model, reducing stockouts to less than 2 percent," Gerberding says. By deploying digital inventory management devices, hiring smart van drivers to stock on a needs-replenishment basis, and providing proper goals and incentives, it is estimated that in 2015 this single initiative saved approximately $325,000 in wasted resources, which doesn't include the financial and societal cost that results from an unintended pregnancy. "This supply chain model is replicable in a lot of other countries with a number of other products, probably even commercially viable ones," she states. "While the primary purpose of these activities is not for commercial profitability, we are not denying that there is business value in having a more effective supply chain." (The company also recently announced an extension of access pricing for its contraceptive implants in Family Planning 2020 countries.)

How Merck Approaches Governance Of CSR

About every five years, Merck conducts a comprehensive assessment of issues that are material or important to both its business leaders and its external stakeholders from a CSR perspective to determine where to focus its efforts. The most recent evaluation affirmed the company's four priority CSR areas — access to health, environmental sustainability, employee health and well-being, and ethics and transparency. "It's not to say we don't address social responsibility issues outside of those four areas, but having this high degree of focus helps us approach CSR in a way that embeds the concept throughout our organization and focuses on those issues that are most relevant," Gerberding clarifies.

At Merck, the office of corporate responsibility (CR) group, consisting of

The Future Of CSR — Beyond Organizational Borders

Whether a Merck corporate social responsibility (CSR) initiative is philanthropic or commercial, one thing is certain — success resides in partnerships. Julie Gerberding, EVP of strategic communications, global public policy, and population health, believes the future of CSR success lies beyond one's own organizational borders. "What I really want to emphasize about CSR is that it's not a set of projects," she contends. "CSR is really a business philosophy of shared values, rather than a philanthropic investment portfolio." According to Gerberding, there are very few important problems worth solving that can be addressed by an individual project or company. "Generally, these opportunities require complex partnerships, sustained large-scale investments, a great deal of patience, and a long-term view," she asserts. "To move CSR to the 3.0 version requires figuring out how individual companies can link together seemingly unrelated projects to make a bigger and more sustainable impact that lives beyond the tenure of the individual leader who championed them in the first place."

This past September, the United Nations launched its new sustainable development goals. One of the philosophic underpinnings of this approach is the recognition that the private sector needs to be actively engaged in driving necessary solutions. "These solutions have to be connected in meaningful ways, rather than a thousand flowers blooming," Gerberding analogizes. "At Merck we have developed a CSR proof of concept that is scalable and transferable, and we are looking to engage with partners with similar CSR interests," she continues. One example of what Gerberding envisions as CSR's future is already taking place — the Pink Ribbon Red Ribbon organization.

Founded in 2011, the Pink Ribbon Red Ribbon program is designed around the already-existing U.S. President's Emergency Plan for AIDS Relief (PEPFAR) system and provides the capacity for clinics to screen for and treat early-stage cervical cancer with very inexpensive tools (e.g., vinegar, liquid nitrogen), as well as introduce human papillomavirus (HPV) vaccine programs for younger girls. "Building these capabilities on top of the already-existing PEPFAR platform, rather than reinventing the initiative as a whole set of other CSR projects, is a much more sustainable mechanism to protect and improve human health," she attests.

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eight people, acts as a central coordinating unit for CSR efforts. Led by its executive director, Brenda Colatrella, this group's role is to learn what issues matter most to both internal and external stakeholders and bring those to the right functional areas within Merck. "The CR group helps guide the conversation with various commercial business units to determine if there are opportunities for leadership, gaps in what we are currently doing or issues that need to be more fully addressed," Gerberding states. Because CSR involves more than philanthropy and corporate giving, the CR group has multiple points of input. For example, CR is part of the strategic communications, global public policy, and population health organization overseen by Gerberding and receives guidance from an advisory council of 15 cross-functional senior leaders, as well as a five-member board of directors subcommittee. In terms of philanthropy, the office of CR is also responsible for Merck's major charitable efforts, both cash giving through Merck and the Merck Foundation and product donations made by the company. While under the CR umbrella of responsibility, the Merck Foundation is governed by a five-member board of trustees to help guide the strategic direction of the foundation and determine the cash grants made on its behalf. This is no small feat. For example, in 2014 alone, Merck and the Merck Foundation gave more than $1.5 billion in cash grants as well as "in-kind" donations through the company's medical outreach program, U.S. disaster relief efforts, the African Comprehensive HIV/AIDS Partnerships (ACHAP), the Mectizan Donation Program, the Gardasil Access Program, and Merck division and subsidiary product donations.

Considering all of these moving parts, determining an overall CSR budget can be very difficult. Merck approaches the challenge as follows. The CR group's philanthropic activities can be broken down into two primary budgets — cash and donations of medicines. While the Merck Foundation is endowed fully by Merck with cash-grant allocations established annually, budgeting for product donation programs requires developing estimates based on forecasted needs. When it comes to budgeting CSR initiatives having possible commercial-related activities, these are normally funded by the business unit responsible for driving the program. Because these funds come out of individual Merck budgets that could be spent on things other than CSR, not only does it create a sense of departmental ownership for the initiative, but also serves as a litmus test for determining the best CSR opportunities to pursue. The Merck CR group also has a separate departmental budget, determined annually, to fund expenses required to maintain the eight employees in their roles (e.g., salaries, benefits, travel, and supplies).

How Not To Let CSR Blur Your Primary Focus

Every company has a finite amount of resources for pursuing its mission. Thus, while pursuit of CSR initiatives can have a positive impact on things like employee engagement or company reputation, unless properly managed, they also can have unintended consequences, such as the loss of primary focus. Don't forget, leaders, by virtue of their roles, have the primary responsibility of first advancing the interests of the organization. "CSR initiatives can create opportunities for learning and partnerships that will ultimately help us," says Gerberding. "While I like being in this space because I get to do the things to bring health to those least enfranchised, the challenge is how to do this in a way that is both really good for our shareholders and patients." To meet this challenge, the CR group uses the following questions to assess and prioritize philanthropic and CSR opportunities:

- Does it address a significant global health need?
- Is it aligned with our business?
- Is it aligned with one of our areas of focus?
- Do we have something unique to bring to the table?
- What type of expertise can we provide beyond just products and financial resources?
- Are there good partners available and willing to participate?
- Can we demonstrate/measure impact?

The last question is perhaps the most important. "While we use the above as a framework for determining what CSR opportunities to embark on, we want to be in a position to demonstrate that resources put into an initiative have yielded significant outcomes," Gerberding affirms. "Don't underestimate the importance of measurement and evaluation. You need to be able to demonstrate progress, impact, and outcomes, because success breeds success."

When it comes to assessing CSR opportunities more closely tied to a commercial space, Merck employs these additional questions.

- Can Merck address the social issue in an innovative way?
- Does it help to build a sustainable business?
- Will this potentially open up a new market?
- Will this provide greater cost efficiencies?

"When considering a CSR commercial opportunity, it pays to do some extra evaluation to make the best match between the social need, our business expertise, and potential business value," she shares.

Merck also has deployed Polaris, a grant–processing system. While Polaris assists the CR group with prioritizing, managing, and responding to various philanthropic opportunities, it also enables generation of required compliance documentation when grants are made, as well as reports to measure progress. "Everything flows through this system so that we can look up a grant or a program we've agreed to fund and see all of the relevant documentation and information," Gerberding says.

When you consider the volume of both CSR and philanthropic requests received by Merck being managed by a team of eight, it pays to prioritize personnel responsibilities as well. For example, within the CR group, a couple of folks focus primarily on philanthropy opportunities, a few focus more from a CSR stakeholder engagement and business perspective (e.g., engaging with socially responsible investors, activist organizations, or other stakeholders), some straddle the two, and one person is responsible for all of the reporting. Obviously, not every philanthropic or CSR request is a fit. In such

cases, whenever possible, the CR group either tries to point the requester in the direction of any organizations they are aware of that focus on that particular social issue or look for other ways to participate. "For example, we have shared our compound libraries to help folks screen their candidates against it to see if there is anything promising," says Gerberding.

How CSR Benefitted A Commercial Opportunity

While the primary purpose of CSR is not for profit, Merck has found opportunities to capitalize on the common ground for what both business and society value. For example, in India there are 15 million people infected with the hepatitis C virus (HCV). "Many patients couldn't afford the cost of HCV treatment," Gerberding relates. To address this growing health problem, Merck Sharpe & Dohme (MSD) India developed Project Sambhav, an innovative microfinancing program for patients with limited or no insurance coverage. Working in conjunction with India financial institutions, the program provides patients with zero-interest, no-collateral loans to be able to pay for Merck's HCV medication, PegIntron, over an extended period of time. In addition, the project included an education component so patients could learn how to better manage their disease.

Since inception, Project Sambhav has expanded to 11 cities across four states in India. According to Gerberding, in addition to addressing an important social need, the program also gave Merck access to a previously inaccessible population. Project Sambhav had a positive financial impact for MSD India while also addressing a significant medical need. But by developing a business rather than purely philanthropic solution, perhaps much more was gained from enabling people to take better care of themselves with a help up instead of a handout. According to Gerberding, Merck's approach to CSR isn't geared toward addressing short-term problems. "We don't do CSR to offset current criticism about things like drug pricing," she concludes. "We do CSR because we are a long-term player. If you want to be in the biopharma business, doing innovative R&D, you have to have a long-term point of view."

Developing A Vaccine For Ebola — A Lesson In Partnering

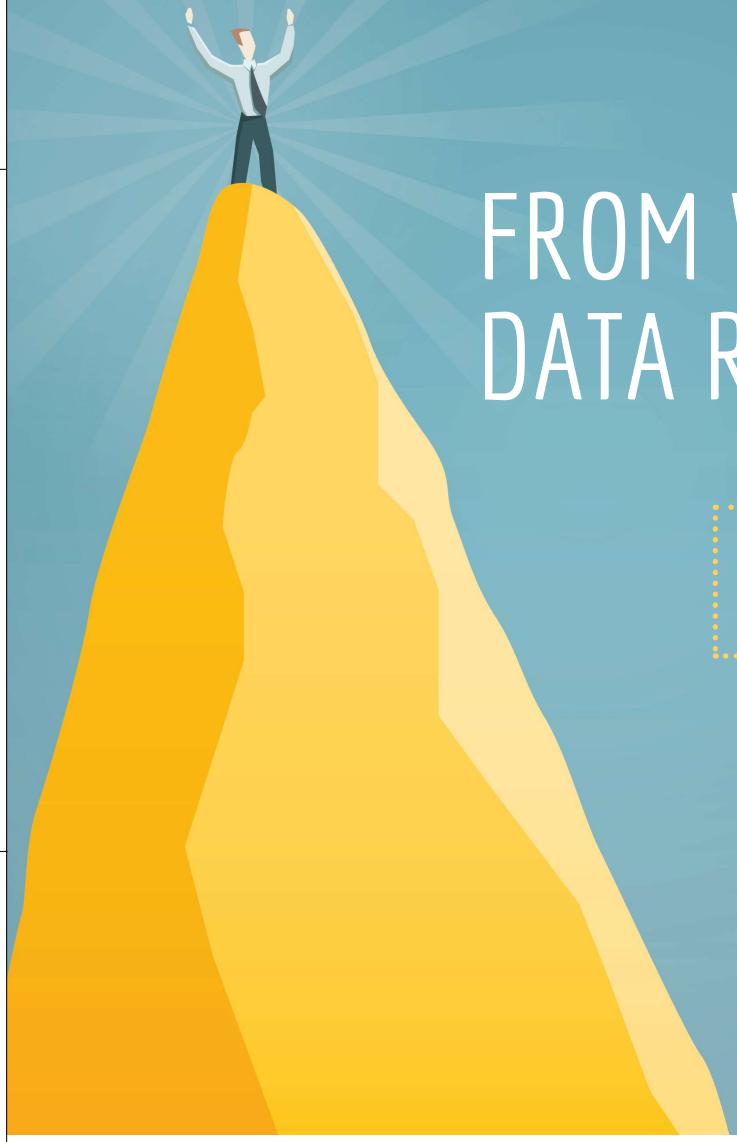
When the Ebola problem was unfolding, one of the first things Merck did in addition to its usual relief efforts was to send two of its infectious disease experts who specialize in infection control to join a Project HOPE (Health Opportunities for People Everywhere) team in Sierra Leone that was tasked with determining a strategy to stop the spread of the virus. "Two of our top medical scientists in the vaccine division volunteered to go as part of a needs-assessment effort to understand what was going on, what were the unmet needs, and what needed to be done," relates Merck's EVP of strategic communications, global public policy, and population health, Julie Gerberding. While those physicians returned with what seemed like an endless list of needs, what was needed most was a vaccine.

Merck was already engaged behind the scenes with NewLink Genetics. "When we learned NewLink had a pretty promising Ebola vaccine and that it was made from the same cell line we use to make one of our already licensed products, RotaTeq, it suddenly seemed feasible that we might be able to do something really fast to address the Ebola problem," she shares. But there were many challenges that needed to be overcome.

First, the two companies needed to develop a licensing agreement. But that was really just the start. "To create a vaccine fast is a pretty 'heavy lift', even with the capability and know-how that Merck had," Gerberding admits. "While we were fortunate that NewLink was a great partner, there were a number of other parties involved, including multiple governments that had to buy into the overarching goal of getting a proof of concept for an effective vaccine on the fastest possible track. We couldn't let the usual bureaucratic or regulatory barriers stand in our way." For example, Merck had to deal with the FDA, while NewLink was dealing with Health Canada. "Bureaucratic challenges extended into Europe, particularly in Germany, as the Germans were doing some of the early safety assessments of the vaccine," she elaborates. "There were all kinds of barriers to importation and other sorts of permissions that typically require permits that can slow things down. But all had the attitude of suspending bureaucracy to move this forward in the safest and fastest way possible."

According to Gerberding, when it comes to moving things along quickly, partnerships matter. "You don't want to be building these partnerships during times of crisis," she advises. "You want to sustain the network of professional contacts." For example, Gerberding trained with NewLink's CEO at UCSF (University of California, San Francisco) and had worked with two other NewLink board members on separate biopreparedness efforts while she was at the CDC. "That's just my little network of NewLink touchpoints," she states. Dr. Gerberding believes that these types of networks are built on scientific credibility, sustained with integrity, and require routine maintenance.

While there were a number of other factors involved in getting the Ebola vaccine to where it is today (e.g., operation, agendas,and planning), Gerberding has one last piece of wisdom. "You need to respect the country experiencing the crisis," she reminds. "We need to be overly conscious of not undermining them, either inadvertently or intentionally." When companies or countries swoop in to solve somebody else's problem, the message sent to their people is that their own government is not competent or is weak. "While this might be the most effective way to move something forward in a crisis, in the long run, it is not the most effective way to solve a problem," she concludes.



FROM WINDOWLESS DATA ROOM AT MERCK TO CEO OFFICE AT INTARCIA

CATHY YARBROUGH Contributing Editor @sciencematter

Kurt Graves, the 47-year-old chairman, president, and CEO of Boston-based Intarcia Therapeutics, got his first major break in the life sciences industry 25 years ago as a sales representative for Merck in his home state of Michigan. In his 18th month on the job, a Merck official asked Graves to arrive in two days at the company's U.S. headquarters in West Point, PA, for a high-priority assignment that could require four months of his time.

Through the company's internal grapevine, Roy Vagelos, M.D., then-chairman and CEO, and other members of Merck's senior team had heard about Graves. In addition to being successful in sales, he was known for setting a company record by completing 16 weeks of sales training in just six weeks. Graves, who had considered attending medical school, attributed his speed in learning about Merck's drugs to his college courses in biology, chemistry, and physics.

At headquarters, Graves worked in the windowless room that housed Merck's scientific data on Prilosec, the company's new treatment for ulcers and gastroesophageal reflux disease (GERD). The FDA had mandated a black-boxed warning on the drug's proposed label, based on preclinical findings of abnormal gastric cells in rats chronically treated with high doses of the drug over their lifetimes. Zantac and other competing, older heartburn drugs did not contain the warning. Vagelos asked Graves to search the files for information that would show whether the black box was warranted for Prilosec's use by humans. If the available data did not support the box's removal, Graves was to suggest how Merck could best educate physicians and consumers about what it meant.

Graves uncovered information that subsequently proved crucial to the removal of the black box in 1995. The FDA's decision, which also was based on human data from the widespread use of the drug, "opened up seven first-line indications which made Prilosec the top-selling prescription drug in the world for many years," Graves recalled.

After completing his assignment, he returned to Michigan to pack his bags to move to Pennsylvania. Vagelos had rewarded Graves with a promotion and a job on Prilosec's marketing team at headquarters. "However, as soon as I moved to West Point permanently, I was sent back into the data room on a new assignment!" he said, laughing. Graves was charged with identifying new ways the pain-relief and healing benefits of Prilosec would clearly illustrate the drug's superiority over competing products. He succeeded and was recognized with the Merck Chairman's Award. Soon he was promoted to lead the business unit for Prilosec.

SUCCESS AT NOVARTIS

In 1993, Graves received another special assignment: work with a handful of Merck executives to build Astra Merck, a joint venture between Merck and Astra AB of Sweden. "Helping build this new company on the back of Prilosec was fun and amazing. I knew then that at some point in the future I would want to do it again," said Graves, who headed Astra Merck's GI business unit until he joined Novartis Pharmaceuticals as senior V.P. and head of the Swiss company's U.S. commercial operations in 1999.

"Novartis had experienced several years of single-digit growth, mostly from price increases, not new product sales," said Graves. Under his direction, Novartis relaunched and repositioned several brands that were underperforming and created a new commercial mindset and infrastructure that was capable of successfully launching the company's new drugs in the U.S. In the early 2000s, Graves and other members of the company's rejuvenated U.S. executive team directed the turnaround and U.S. launch of multiple new drugs. Novartis began a four-year period of 20 percent annual growth.

Impressed with the turnaround in the U.S. operations, Novartis' global leaders persuaded Graves to instill in Europe and Asia the insight-driven approach to marketing, drug development, and branding that he had implemented in the U.S. In 2003, Graves moved to Novartis' worldwide headquarters in Switzerland as the company's first chief marketing officer and head of the general medicines business unit.

After five years as a member of Novartis' global executive team, Graves was ready for a change — and the opportunity to help build an entire company as he had done earlier in his career at Astra Merck. That meant leaving Big Pharma so he could get his hands on the many different levers that drive a company's success. In 2007, he joined Boston-based Vertex Pharmaceuticals as the early-stage company's first executive vice president, chief commercial officer, and head of corporate development and strategic drug development. The company's pipeline then included a hepatitis C virus (HCV) drug in clinical development and two preclinical cystic fibrosis (CF) drugs, one of which is Kalydeco, the first FDA-approved drug for CF. "It was a very exciting time for Vertex," Graves said.

After two-and-a-half years, Vertex had grown from $1 billion to $8 billion, but Graves was not happy. "While Vertex had great medicines coming through the pipeline, it turned out to be quite a bit different from what I was looking for," he said. "There was a series of rapid and unplanned changes at the board and CEO level, and at the same time the company wasn't making some strategic moves on the HCV front that I and a couple of others felt were key for winning long-term."

LOVE IT, CHANGE IT, OR LEAVE IT

"One of the biggest changes I wanted to make on a key executive hire in HCV got shot down by the head of R&D and the CEO for the wrong reasons, and that proved to be a fatal mistake for Vertex in HCV," said Graves. "With all of the changes and resistance, I realized I was still working on important medicines, but I wasn't having fun, and after 20 years in Big Pharma, I was looking for a different culture and far less politics. It's moments like that when you have to decide whether to love it, change it, or leave it. I think it's a really healthy thing to know when to move away when something doesn't fit, both for yourself and the company."

"HAVING MORE SALES REPS THAN YOUR COMPETITORS HAS BEEN THE COMMERCIAL MODEL FOR MANY YEARS, BUT THAT MODEL IS SERIOUSLY BROKEN."

KURT GRAVES
President & CEO, Intarcia

After leaving Vertex, Graves did not immediately search for a job but for knowledge — he wanted to understand how biotech companies operate and are funded. He met with numerous biotech entrepreneurs and venture capital and private equity officials. "I was astounded by how much innovation occurs in biotech companies and academia," he said. "Truly disruptive technologies and products tend to come from smaller, faster, more flexible, and more innovative companies not tied to the business models of the largest pharmaceutical firms."

For his next position, Graves was determined to find "something special, a once-in-a-lifetime opportunity." He decided to seek board positions that would enable him to fully assess five early-stage companies from the inside. To identify the boards he wanted to join, Graves systematically evaluated more than 50 biotech companies. He agreed to serve as executive chairman of Radius Health and Intarcia Therapeutics, the two companies "that I loved the most," he said.

In 2010, Graves was introduced to Intarcia by Bryan Roberts, Ph.D., whose firm, Venrock, had invested in the company. "Bryan was leading the charge for change, knowing the runway wasn't going to last much longer," Graves said. At

Roberts' request, Graves spent one week at Intarcia. "I did full due diligence and came back to the board with my thoughts and recommendations for change," he said.

"While the company was clearly struggling, the more I dug into it and learned about its technology, IP, and early clinical data, the more excited I became," he said. "After a few days of connecting new ideas and seeing new possibilities, I told Bryan that Intarcia's technology could be the most exciting platform that I've ever seen." The company had determined how to stabilize therapeutic proteins, peptides, and antibody fragments at human body temperatures for extended periods of time. The technology provided a possible new route for once- or twice-yearly drug administration.

At the board's request, Graves agreed to serve as executive chairman. "I wanted to do more diligence, meet potential partners, get to know the team, and meet with the FDA to see if the early vision I had was possible or not," he said. "I fell more and more in love with the company and our possibilities." In 2012, he agreed to serve as full-time chairman, president, and CEO because of the "potential to open up a new category of disruptively innovative once-yearly therapies for chronic diseases, therapies that could deliver a real win-win set of outcomes for all of our stakeholders, patients, payers, providers, and shareholders."

THERAPY ELIMINATES PATIENT NONADHERENCE

Intarcia's late-stage investigational product for type 2 diabetes, ITCA 650, is a tiny matchstick-size osmotic mini-pump that is placed under the patient's skin by a trained physician or nurse. For up to one year, the mini-pump delivers a continuous, consistent amount of exenatide, which is now administered by frequent self-injections as the FDA-approved AstraZeneca medications Byetta and Bydureon. "In type 2 diabetes, 70 percent of patients don't adhere to their therapy after just six to 12 months, and that is when bad things can happen," Graves said. Intarcia will file for regulatory approval for ITCA 650 in the U.S. and EU in 2016. If patients and physicians have positive experiences with ITCA 650, the company's mini-pump technology could be adapted for the treatment of other chronic diseases characterized by high levels of patient nonadherence.

Graves emphasized the importance of each individual's experience with ITCA 650. "I've helped launch over 20 drugs, and with each one, I've found that a physician's opinion about a new therapy is primarily determined by the experiences of the first three to four patients," Graves said. "How well those patients do is one of the most important things that I've learned about the success or failure of a new therapy." In his first meeting with Intarcia's board, Graves proposed the creation of an officer-level position titled Head of Customer Experience and Outcomes (CXO).

"When you have a disruptive and innovative medicine in a category like diabetes, you must do everything from day one to optimize training, identify and implement best practices, and continuously enhance technologies to optimize the entire customer experience right from the start," he said.

The CXO's first assignment was to work with two Boston-based engineering firms to design a novel placement tool that would insert the exenatide-loaded mini-pump under the skin as fast and flawlessly as possible. Three years ago, an average 12 to 15 minutes was required to complete the procedure. "Now it can be done in less than one minute," said Graves. The error rate of physicians and nurses trained to insert and remove the pumps has been reduced to less than one percent. "The CXO and his team are developing next-generation placement and removal technologies that will continue to improve the customer experience," he said.

Unlike most biotech companies, Intarcia has not depended on Wall Street and public investors for the substantial monies required to conduct and complete global Phase 3 clinical trials, submit regulatory filings, and commercially launch a new

"WE PROACTIVELY STAMP OUT POLITICS"

Soon after taking the helm at Intarcia Therapeutics, Kurt Graves organized a leadership team retreat to identify the company's vision and core values. Trust was one of the six values that the group agreed upon, and one of the qualities that Graves and his colleagues used to define trust was a strong aversion to office politics and personal agendas.

"We proactively stamp out politics at our company," said Graves, whose almost 25-year career has included executive positions at Merck, Astra Merck, Novartis, and Vertex, as well as the privately held Intarcia.

Graves added, "How a leader guards against political agendas means everything to a company. If a CEO allows office politics to exist, the company's values are undermined, and the culture is certain to get bad. The only question is, how bad?" Turning a blind eye to office politics can result in backroom alliances and decisions, nontransparent agendas, a proliferation of bureaucracy, unhealthy competition among staff, and most importantly, a general loss of confidence in the workplace as a trustworthy environment, he said.

On the second day of the leadership team retreat, the 47-year-old Graves asked the leadership team to "put our values into action," by assessing how the staff of the Boston-based company fit the newly established values. A few staff members did not score high on trust. "Although their individual job performances were good, they were holding us back and not acting in the best overall interests of the company. They were creating issues and not unleashing the full potential of the staff around them," he said.

Staffing changes occurred at every level from officers to managers. "It made a huge impact on our corporate culture far more than just hanging posters on the wall and talking about it," Graves said. "These changes were necessary for us to advance. We have far too much to accomplish to lose our sense of urgency, passion, and tenacity by allowing bureaucracy and politics to creep into our operations."

therapy. Intarcia instead secured more than $1 billion from private financing and novel deals and partnerships and more than $1 billion in up-front and potential milestone payments from its partnership with the independent French pharmaceutical company Servier, which obtained the commercialization rights to ITCA 650 worldwide.

NO IPO ... YET

By not pursuing an IPO, Intarcia has retained complete strategic and financial control of ITCA 650, and the company's senior team does not have to spend a significant portion of its time "on public-company topics that can be highly distracting," said Graves. "At some point we will become a public company." Intarcia could consider an IPO after regulatory approval and the full launch of ITCA 650 and once additional products are added to its pipeline. These significant accomplishments should strengthen Intarcia's valuation and thereby boost considerably its public offering price.

Large global pharmaceutical companies currently dominate the type 2 diabetes market. Graves is often asked whether Intarcia will compete by hiring more sales representatives than the Big Pharma companies have for their type 2 diabetes drugs. "If ITCA 650 were a pill or injection, we might hire lots of sales reps to compete for market share. Having more sales reps than your competitors has been the commercial model for many years, but that model is seriously broken," he said. "Today we live in a healthcare environment in which payers have the most control, and payers are focused on the aggregate facts including overall patient benefit or outcomes and impact on healthcare costs."

So instead of hiring 2,000 sales reps, Intarcia is funding five head-to-head superiority trials comparing ITCA 650 to current standards of care for type 2 diabetes. Top-line results of the first head-to-head Phase 3 trial were announced in August 2015. In the 52-week study, ITCA 650 was shown to be more effective than Merck's market-leading oral Januvia in achieving glucose control and weight loss.

"The results of these clinical trials will show our differentiated value proposition to payers, and they will then help us drive appropriate use of our medicine with physicians and patients," he said. "Many leaders strive only for incremental differences or less, which leaves you in a position without any evidence of real advantages that will matter to payers, patients, and providers. Real differentiation, for payers in particular, demands much more."

Graves continues to fall in love with companies. His latest is Seres Therapeutics, which announced in November 2015 that Intarcia's chairman, president, and CEO joined its board. Graves also serves on the boards of both Achillion Pharmaceuticals and Pulmatrix Pharmaceuticals and chairs the boards of both Radius Health and Intarcia. L

AMARANTUS: RISEN FROM THE ASHES

THE ENTERPRISERS

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

PRIVATE/PUBLIC (OTC)

MARKET CAP: $16M (12/7/15)

CASH: $278K at 9/30 (additional financings totaling $700K)

STARTUP DATE: January 2008

NUMBER OF EMPLOYEES: 9

FOCUS: Discovery and development of orphan drugs, diagnostics, and artificial skin

A simple twist of fate is all it takes to knock you off your original track. In the case of the company that would be reborn as Amarantus, it was another company's bad luck in the clinic that ended its first push for partnering and funding. Gerald Commissiong, president and CEO, recounts how his father's earlier Canadian startup fell after a trial of Amgen's competing compound for Parkinson's disease failed. "Amgen was unable to deliver the drug to the right location in the brain, and therefore investors felt, if Amgen couldn't succeed, my father's company would not either," he says.

The compound was MANF (mesencephalic-astrocyte-derived neurotrophic factor), a difficult delivery challenge that did ultimately prove insurmountable for the smaller company with dwindling funds. The company was Prescient NeuroPharma, founded by Dr. J.W. Commissiong in 1999 and burned out in 2003, leaving its core IP for the lead compound and discovery platform for neurotrophic factors, PhenoGuard, sitting in ashes.

It would be five years before the younger Commissiong recovered the IP from Prescient and fired up a new version of the original enterprise — with significant enhancements. Not only has the new company found an apparent solution to the delivery problem with MANF, it has also broadened its development program and added several other therapeutics to its pipeline, as well as a diagnostics business and an artificial skin product. Those additions are attracting funds to Amarantus that give some support to the MANF program, now ramping up to Phase 1 trials for Parkinson's and two rare but critical eye conditions.

But for years after its founding, failure to achieve a delivery solution for the product's use in Parkinson's continued to plague the company, so along with refocusing the MANF program on ophthalmology, Amarantus made the move to diversify generally, according to Commissiong. It was an opportunistic strategy, he says — mainly acquiring assets that came up through the relationships he had built in putting the company together — but, at least initially, the in-licensing stayed close to the company's roots in Parkinson's, though it began with diagnostics.

"There's a story behind every product and every acquisition," says Commissiong, relating how the company began and expanded its diagnostics line. "We were in the Parkinson's space. We had already licensed a diagnostic for Parkinson's, believing there was a lot of interest in peripheral diagnosis of neurological conditions using biomarkers. In Parkinson's, our biomarker was a series of proteins, or protein signature. Then, as we improved our understanding of a diagnostic opportunity, we saw Alzheimer's as a much larger opportunity and a much greater medical need. And so we diversified into peripheral diagnosis of Alzheimer's." In a separate division, Amarantus Diagnostics, the company has commercialized its Alzheimer's diagnostic for research, LymPro, and also is developing the MSPrecise diagnostic for multiple sclerosis.

Next, the company brought in eltoprazine, a small molecule 5HT1A/1B partial agonist, now in late-stage development for treating Parkinson's disease levodopa-induced dyskinesia (PD-LID) and adult attention deficit hyperactivity disorder (ADHD). Eltoprazine had been thoroughly tested in preclinicals and human safety trials by a series of owners — Solvay, then Abbott and PsychoGenics — before Amarantus licensed it and took over its development. The compound is also ready to move into Phase 2 development for Alzheimer's aggression. Amarantus asked the FDA to grant orphan-drug status to eltoprazine for the PD-L1D indication in October 2015.

Artificial skin was another matter entirely. For the first time, Amarantus bought an entire company, Cutanogen,

> "Having a pipeline that covers multiple scientific and disease areas is a big advantage because of cross-pollination."

GERALD COMMISSIONG
President and CEO, Amarantus

to obtain Engineered Skin Substitute (ESS). ESS is a regenerative medicine product made by starting with a patient's own skin tissue to culture an epithelium, or outer sheaf of cells, together with a collagen-fibroblast implant to replace the epidermal and dermal layers of the skin. ESS is entering a Phase 2 clinical trial with the U.S. Army for treatment of severe burns in adults, treating soldiers with full-thickness burns covering over 50 percent of their bodies.

Commissiong says various versions of ESS have been used in the treatment of more than 140 pediatric patients at the Shriner's Hospital in Cincinnati, with impressive results. A presentation to the FDA in 2012 showed a reduction in mortality of more than 25 percent and a significantly faster time to full wound closure in a 16-subject, compassionate-use study.

"Right now we are targeting burns because there the primary problem is loss of skin, in which you are completely immunologically compromised," he says. "Reestablishing that barrier is paramount to survival and to limiting infection, which has its own set of consequences."

Along with the product, he says, Amarantus also acquired strong data in the use of ESS in congenital hairy nevus, an inherited disorder creating what amounts to a giant mole over a large percentage of the body that can sometimes become cancerous. "You do a skin graft on a 6-9 month-old patient, and follow up 13 years later, to find the skin replacement has grown and the child has never had to go through another revision surgery, so that patient is effectively cured of the condition."

These days, the company is strongly inclined to sell or spin off its diagnostics business. Commissiong says the unit will be bringing in "much more qualitative revenue than quantitative revenue in the near-term," and the revenue will be insufficient to support therapeutic portfolio development, which is much more expensive than developing diagnostics. The move to make the diagnostics unit separate and independent from Amarantus may also be good for the neurodegenerative-disease space in general, as more and more developers concentrate on detecting and treating the disease as early as possible.

FOUNDING ACTION

For all of its therapeutics, Amarantus has so far concentrated on orphan indications, but the company also shows a strong willingness to apply each product's mechanism of action (MoA) as broadly as possible over time. And the best example of that is still its original drug candidate — MANF. The particular neurotropic factor appears to be active in a host of related, and in some cases seemingly unrelated, conditions and disease areas, perhaps because its MoA is essentially to correct protein misfolding.

"MANF acts like a chaperone and basically helps cells get through times of stress, whether from injury or disease," says Commissiong. "There are also some other interesting components of the growth factor related to neurotransmitters — a receptor mechanism that modulates the action of calcium channels." It also appears to protect injured cells, as in reperfusion events, by interfering with the apoptosis pathway, according to the company.

"Having a pipeline that covers multiple scientific and disease areas is a big advantage because of cross-pollination," he maintains. "It's not usually about indication, it's about mechanisms, and those mechanisms get applied across many diseases. For example, working on our diagnostic blood test for Alzheimer's disease gives us tremendous insights into the immune system, therapeutic avenues, tissue generation — many things going on in the body that are not well-known. Our neurotrophic factor has a broad swath of potential applications, so that has led us into science in numerous areas. It's interesting to see them all interplay with one another."

In fact, the list of current and prospective pipeline indications for MANF is quite long. The lead program is for retinitis pigmentosa (RP), the name for a set of congenital diseases that can lead to blindness by causing the retina to degenerate. But, in addition to other conditions in the eye and specific neurological indications such as Parkinson's disease and traumatic brain injury (TBI), the company envisions possible future programs for various conditions in diabetes, ischemic heart disease, and Wolfram Syndrome.

Commissiong points out the importance of delivery technology as a distinguishing factor among the variety of applications possible for a single protein such as MANF. With biologics, each indication may require a different drug-device combination — in effect, a different product. In the research phase, the emphasis is on defining the drug mechanism and how it might affect the symptoms of various diseases. But once the drug enters the commercialization stages, the developer must select or create a mode of delivery that will accommodate the specific condition, patient needs, practice setting, and so on. Then clinical trials will test the

drug's ability to alter the disease state and cause functional improvement.

To solve the delivery problem for the Parkinson's program, Commissiong says the company found a "better mousetrap" at the University of Bristol in the work of a famous neurosurgeon, Steven Gill, who overcame a lot of the deficiencies of previous direct injection to the brain technologies. Gill recently published the results from Amarantus-funded animal-model research showing his method appears to deliver the MANF protein to the brain in the right quantities and infuse the key areas without leaking into the surrounding areas. "Now we have a good handle on what it will take to translate the technology into human use," Commissiong says.

Meanwhile, he adds, the lead strategy for MANF is to stay focused primarily on orphan ophthalmological indications. "We like ophthalmology because we're talking about direct injection to the eye, a discrete organ where we use really small quantities of the drug, so there is limited toxicology risk. Our strategy is to bring a product to market as quickly as possible that can address a key unmet need in the ophthalmology space, where there are a lot of unmet needs."

Commissiong says the second ophthalmology program for MANF, retinal artery occlusion (RAO), is basically a ministroke of the eye requiring similar urgency. "Much like a regular stroke, time-to-treatment is absolutely paramount for RAO because the occlusion leads to downstream effects, so the delivery may be drastically different than with a long-term condition like retinitis pigmentosa." FDA has granted orphan-drug status to MANF for the RAO indication, and both the FDA and the European Union have placed their respective orphan designations on the compound for treating retinitis pigmentosa.

Despite, or maybe because of, the wide range of possibilities for MANF, its development is still in the early stage. But Commissiong says the company is establishing a GMP manufacturing process for the protein and expects to be in the clinic with the growth factor in 2017.

Looking further into MANF's future, he sees gene therapy as one possible alternative "delivery" route. "Gene therapy has a lot of promise. We haven't done anything yet, although we may seek to partner that out because there are so many capabilities required in gene therapy we just don't have. Replacing missing or defective genes is probably a winning strategy, but it remains to be seen whether it is a durable, long-lasting technique. Using it as a method just to deliver a protein that has some important, but maybe ancillary, benefit is probably much more challenging, largely because you're infecting sick cells."

FUTURE POSITION

Turning from the view ahead to the view behind, Commissiong also gives a good account of where the company stands right now. "We started a company that needed improvement in its intellectual property. We built a tremendous portfolio of IP for MANF, not only around composition of matter, but various and intertwining uses that really create a strong position in the MANF space. So I think it would be very challenging for anybody to try to develop products in the space without coming through us." He has equal confidence in the company's IP position for its other assets.

On the MANF development side, however, Commissiong rates the progress as slow. "GMP manufacturing of biologics is time-consuming and expensive, and it's difficult for a company our size to marshal the needed resources unless it is VC-funded — that has been our challenge," he says. "As an over-the-counter public company, we're in a sort of no-man's land, so funding has been sporadic. We're not private, so we can't really access private sources of capital, but we're not truly public because we're not on the NASDAQ. The larger investment funds can't invest on the OTC market, so we have had to take funding from various hedge funds to keep us going."

Amarantus has raised about $40 million total, $30 million since late 2014. "A lot of our funds have gone toward product acquisitions, and now we have a tremendous portfolio that we want to advance through value-building milestones as we go forward," Commissiong says. Of note, the company has received significant grants from the U.S. Army, for the ESS program, and patient associations such as the Michael J. Fox Foundation for MANF in Parkinson's disease.

Commissiong cites an industry veteran on his board of directors, Joseph Rubinfeld — one of the founders of Amgen and inventor of amoxicillin — on how a company can endure and prosper in the life sciences industry. "This is a tough business, but Dr. Rubinfeld's advice is always, 'If you can stay on the playing field long enough, and you have the right assets, eventually the company will succeed.' Three years ago all we had was the preclinical data in neurotrophic factors. Today, we have the skin product moving into Phase 2 for adult burns and probably moving to Phase 3 trials for congenital hairy nevus and pediatric burns in the second half of next year."

Durability plus assets equals success. It's a simple formula containing thousands of variables and constant perils. But for this company that has seen the fire and risen from the ashes, all things now seem possible. L

Do you have something to say about Amarantus and its MANF delivery solution and expanded pipeline? Please post your comments online with this article under Current Issue (January 2016) or Past Issues at lifescienceleader.com.

J&J Hopes To Change The Paradigm
On Compassionate Use Review

ED MISETA Executive Editor @OutsourcedPharm

Expanded access, also known as compassionate use, is a subject that can stymie many pharmaceutical companies. The terms refer to the FDA program allowing pharma companies to provide patients with an investigational new product outside of a clinical trial. This might occur when a patient does not qualify for a clinical trial or there is no ongoing trial.

The decision of whether or not to make an investigational drug available to a patient can save a patient's life, cause adverse health effects, or result in a firestorm of controversy on social media. Most companies handle the approval of compassionate use requests differently, and few likely enjoy reviewing these requests or making these difficult decisions.

For that reason, Johnson & Johnson made headlines over the summer when it decided to undertake a pilot program to change its compassionate use approach, opting to have an independent review panel consider requests made to the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen) for compassionate use of an investigational medicine that was undergoing clinical testing and was in short supply. For this pilot, requests for the medicine, Daratumumab, a treatment for multiple myeloma, were independently reviewed by a committee of internationally recognized medical experts, bioethicists, and patient representatives convened by the New York University (NYU) School of Medicine.

Dr. Amrit Ray, Chief Medical Officer (CMO), Janssen, has spoken to enough patients and had enough involvement in compassionate care decisions to know that a better system was needed for helping those people seeking access to investigational new drugs outside of a clinical trial. After many sleepless nights considering the challenges faced by patients and how the situation could be improved, Ray and J&J decided to stand up and stand out to drive a positive change and went to work.

"One of the most important things I learned as a physician is the importance of active listening," says Ray. "We have listened to patients and their families on the question of compassionate use. They have told us that it is a very poorly defined area in general across all companies. Patients and their families often have many questions that they are not able to get answered. Questions related to topics such as how the process works, who they should contact, what information they need to provide, and how companies decide who will be provided access to a medication. When we stepped back and reflected on that, it was clear we needed to have a better process in place."

SIMPLIFY THE PROCESS

In some biopharma companies a compassionate use request might come in through one of many different avenues, get forwarded to numerous individuals within the company, and end up with a physician involved with the medication or its clinical trials who will then decide whether to approve or deny the request. The requests might not always be handled in the same manner or by the same person. This inconsistency and variation in the process from one company to the next only increased the need for some type of structure to be deployed.

But other factors also contributed to J&J's decision to move the review to an independent committee. "We can all see the feedback from patients that has come in the form of heart-wrenching media campaigns," notes Ray. "Sometimes these campaigns might involve a half-million petitions. Additionally, Right To Try laws have now been passed in 24 U.S. states, and there are also discussions taking place

at the international level in groups like the World Health Organization (WHO). That tells us there is a real societal need for a process that is fair and ethical and considers the needs of patients and their families in a more purposeful manner."

CREATION OF TASK FORCE LEADS TO INDEPENDENT PANEL

In April 2014, Johnson & Johnson took the first step toward addressing these concerns and launched a dedicated Pre-Approval Access Task Force sponsored by the J&J Office of the Chief Medical Officer and empowered to take an in-depth look at the process J&J had in place. The task force, composed of leaders and colleagues from across the company, considered aspects of the process end-to-end and looked at numerous perspectives, including the needs of patients, regulatory concerns, and clinical development. The goal for J&J was to be objective and take an ethics-based, evidence-driven approach to what could make a real difference for patients.

When the idea of an independent review panel was proposed, the task force looked at several different options before landing on NYU. The responsibility for choosing panel members was left to NYU. A key goal was ensuring that potential panel members would not have any conflict of interest.

"The NYU School of Medicine set up a compassionate use advisory committee, which we refer to as CompAC," says Ray. "The committee is made up of 10 internationally recognized bioethicists, medical experts, and, importantly, patient representatives. They reviewed the compassionate review requests for Daratumumab and did so for several months. Once they performed the review, they returned to J&J with their recommendations. We continued to take full responsibility for the final decision on whether or not to approve the request. In almost all cases, we agreed with the recommendation of the committee." The committee reports directly to NYU, and the school receives a fee for the administration and work of its committee members.

A preapproval access decision must take into account information such as what data is available on patient safety and efficacy, populations that responded well to the medication, and the often limited availability of clinical supplies.

INNOVATION ALSO CREATES CHALLENGES

This program was designed to make compassionate use interactions easier for physicians and patients, thereby creating a new model for researchers and industry. To accomplish those goals, J&J had to figure out how to balance a multitude of factors such as evolving safety and efficacy profiles, the constantly evolving body of scientific information, the supply challenges that exist for all investigational medicines while they are still being developed, and the regulatory considerations around compassionate use.

"We made sure we thoroughly scrutinized and addressed every challenge that arose in this debate," states Ray. "We did that using expertise both inside and outside the company. The outside input came from many sources including bioethicists, patient groups, and the NYU experts. In fact, NYU was constantly evaluating our model to make sure we were moving the pilot forward. We also shared the pilot idea with the regulatory authorities so they were aware of what we were doing."

Throughout the process, Ray kept track of the challenges he encountered to make sure his team was able to learn from them. He felt these learnings would also contribute to a stronger model in the long term.

DEVELOP AND OPERATIONALIZE ETHICAL PRINCIPLES

There were two main goals J&J had in mind when investigating this change. "Number one, and most importantly, we knew we needed to develop a set of bioethical principles that would guide the decision making," says Ray. "That has been done. We have agreed on the following six principles:

1. **Beneficence** – Moral imperative to help patients
2. **Equality** – Ensure process that treats all patients in a just and fair manner
3. **Evidence-Driven** – Diligent assessment of risk and benefit in decision making
4. **Patient-Focused** – Consideration of patients' perspectives, including timely communication
5. **Transparency** – A process that ensures that information important to patients is understandable and accessible
6. **Holistic View** – Considering both individual need and societal benefit in making safe and effective drugs available

The second goal has to do with how those bioethical principles are operationalized and relates to the processes, technologies, expertise, and commitment within large, complex, and global organizations, to ensure that decisions are made in a consistent, thoughtful, and timely manner. Ray believes the CompAC pilot will help J&J accomplish both goals.

COMPAC SIMPLIFIES THE PROCESS FOR PATIENTS

According to Ray, the new process utilizing the CompAC panel significantly simplified the process. His team members put themselves in the shoes of the patients to figure out the best ways for their physicians to apply for use of a product. The company also directly asked a number of patient groups for feedback on what would be helpful to them and for their advice on how the process should work.

The new process allowed compassionate use requests to J&J to be submitted either via a specialized 800 number or through a dedicated email address. Both the phone number and email address were available on the Janssen website. In addition, to further help those families pursuing expanded use of a drug, on its website J&J lists the key principles relating to its compassionate use policy and offers a short video that explains what patients and families should expect during the process. Most importantly, it offers clear guidance on how patients can work with their physicians to submit expanded use requests.

One of the most frustrating situations a person can encounter is submitting a request to a large corporation and then never hearing anything back. To avoid this situation, J&J has also made a commitment to always close the loop with patients through their requesting physicians.

Ray states this is one of the biggest frustrations that he personally heard from patients. "Listening to patients who have interacted with many companies over time, they would submit a request but would often not get a response," he states. "When they did get a response, it was often unclear to them why there was a denial. With the efforts that we are taking, we are making a commitment to patients to ensure that there is always clear, respectful information provided back to patients in a reasonable timeframe."

MOVING BEYOND J&J

In November of 2015, J&J received approval of Daratumumab from the FDA, and it will be sold under the brand name Darzalex. With that approval, the pilot study came to an end. Although Ray could not reveal the exact number of requests that were received, he notes the pilot received positive feedback from stakeholders involved in the process, including patients and patient groups. J&J and NYU are both committed to an open pilot and publishing the findings for anyone to see. Their hope is that this pilot could be used as a model by other pharma companies and will be considered a positive step for public health.

"It was clear we needed to have a better [compassionate use] process in place."

DR. AMRIT RAY
CMO, Janssen

For now, J&J is performing an independent audit of the pilot. That audit will take place over the next few months. If it is deemed to have been successful, it will be applied more broadly across the portfolio of the company. Any improvements recommended by the audit will also be considered.

Despite the best intentions of Ray and his team, there will still be detractors who believe this committee is nothing more than an attempt by J&J to take a difficult decision-making process and outsource it to an outside entity. Ray notes nothing could be further from the truth.

"When you look at what we went through to develop this pilot, you can clearly see that our primary consideration was always to do what was right for our patients. With compassionate use, patient lives will always be on the line, and that decision-making responsibility is something we take very seriously. We continue to be fully responsible for getting to the right decision on patient requests. Taking the time to develop a process that is fair, consistent, thoughtful, and patient-centric is important to every stakeholder in this process," he concludes.

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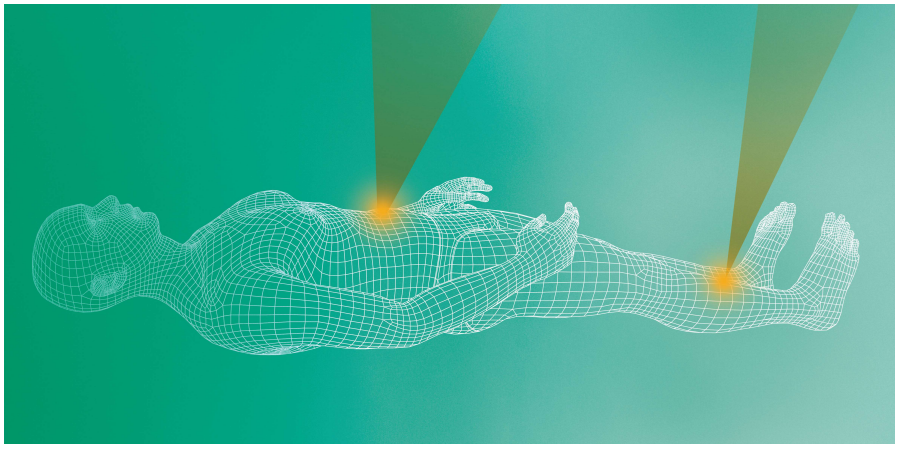

Michael Benchimol doesn't want to compete with "conventional medicine." At least not yet. The founder and chief technology officer of Sonrgy, Inc., a nanotechnology drug-delivery start-up based in San Diego, says, "Some in the pharma industry still view nanomedicine as *competitive* to their efforts. Instead, we are complementary to products they're developing. Nano can build on existing therapeutics in completely orthogonal ways to open new doors for patients."

Orthogonal ways? "I'm referring to how nanomedicine can change the distribution of a drug without altering the chemistry of the compound," he says. "This type of independent control over the kinetics of a drug is orthogonal. Basically, we *leverage* the great work pharma scientists have put into developing their compounds and build on that success for patients."

Now *leverage* ... I get. And as stated in a first article on nanomedicine in the September issue of *Life Science Leader*, we all should understand nano as a legitimate and growing segment of the biopharmaceutical sciences. Benchimol is optimistic: "More people are coming to realize the opportunity in taking a collaborative approach. Pharma is actively looking at enhancing their existing line of compounds and embracing nanomedicine as a part of that."

Sonrgy is doing its part specifically by leveraging advanced ultrasound technologies to "burst" — or release — existing anticancer agents from nanocarriers (drug-loaded capsules 100 times smaller than our own blood cells) encapsulating these drugs. Simultaneously, Sonrgy utilizes the ultrasound's advanced imaging to accurately monitor the treatment at the cancer tumors. Benchimol says the initial drugs Sonrgy is combining with its nanocarriers are well established generics known to be active against pancreatic and liver cancers, two of the most difficult-to-treat cancers in humans.

Here's how Benchimol sees his business and technology — and the continued acceptance of nanomedicine — progressing over time.

NANO COMING TO THE DOCTOR'S OFFICE

With the advent of ADCs (antibody-drug conjugates) and various other delivery systems — including some nano-applications — for cytotoxic agents, we have reached a point in the history of medicine where technologies and products readily make use of the biochemical targeting of tumors. Sonrgy, however, takes a different tack. It's decided not to employ biochemical targeting with the nanocarriers it has in development. "This allows the technology to work independently of a tumor's biochemical profile," explains Benchimol. The Sonrgy strategy is to use nanocarriers that remain circulating within patients for extended periods (and are composed of lipids), aided by ultrasound focused directly on tumors, "so the nanocarriers are releasing the drug payload directly into the tumor's capillary bed ... and not in other areas of the body where they can cause damage to healthy tissue."

Benchimol, who holds a Ph.D. in ultrasound-responsive particles for cancer diagnostics and therapeutics and an MS in photonics, believes that in the near future, patients with these difficult-to-treat cancers will be able to lie on a bed in a doctor's office or at a clinic and receive an infusion of the Sonrgy drug formulation (i.e., medicine inside

"Pharma is actively looking at enhancing their existing line of compounds and embracing nanomedicine as a part of that."

MICHAEL BENCHIMOL
Founder and CTO, Sonrgy, Inc.

nanocarriers) while receiving ultrasound. "It would be an outpatient procedure," says Benchimol. "Similar to a typical chemotherapy regimen today, the treatment might be repeated to maximize efficacy so patients enter a more manageable disease state, including potentially downstaging patients so they can become candidates for surgery." However, to be clear, before that scene plays out, more formulation development and technology design, ultrasound and nanocarrier enhancements, and of course clinical study, need to be accomplished. Here's the business plan.

ADVANCEMENT AND RECOGNITION

Sonrgy was formed in 2012 by Benchimol, his Ph.D.-advisor Sadik Esener, and another scientist at University of California San Diego, Chris Barback, who currently serves as Sonrgy's head of Preclinical Ultrasound. Two years later, Brian O'Callaghan and David Renas were brought in to bolster the team. "I've worked exclusively in the technical and scientific field, and wanted to bring in business expertise to help navigate the field of pharmaceuticals," says Benchimol. O'Callaghan has worked in a number of brand-name Big Pharma and smaller companies. Renas previously served as CFO and general counsel of Sangart, Inc., a biopharmaceutical company focused on the development of oxygen therapeutics.

Regarding the Sonrgy business model, like most start-ups nowadays, the company outsources as much as possible. However, it performs its own formulation testing and manufacturing — encapsulating the medicine into the nanocarriers — in its lab in Sorrento Valley, a tech/biotech hub in San Diego. And of course drug delivery companies like Sonrgy are natural partners for companies that own or discover new drugs. Sonrgy collaborates with Histogen, Inc., a biopharmaceutical company developing novel agents, to investigate the delivery of Histogen's proprietary agents using Sonrgy technology. In this type of relationship, Sonrgy and its nanocarrier platform can enhance the performance of the agents, as well as potentially find ways of extending patent protection. And, as you would expect, Sonrgy is also working closely with a leading ultrasound device manufacturer to help develop and combine technologies. This provides Sonrgy the opportunity to test its material with an ultrasound system and interface already widely available at medical centers.

"For a long time people didn't recognize the opportunity to precisely control the release of drugs *externally*," says Benchimol. Those that did encountered challenges, including "a struggle to create a nanocarrier that remains stable long enough to hold onto its drug until it reaches the tumor location." Benchimol believes his is the first technology to overcome this hurdle and also maintain all the necessary pharmacological properties proven necessary for a new drug. "It's this combination of properties that sets us apart," he says.

When I ask Benchimol about the promise of ADCs, his reply is similar to that of Laurent Levy, CEO of the Paris-based, oncology-focused nanomedicine company Nanobiotix, in the earlier article on nanomedicine I mentioned above. Their opinion is that nanotechnology will enhance the ADC platform. "ADCs are an exciting area; there have been successes, and there are more to come," says Benchimol. "However, ADCs typically target specific subpopulations of patients who express a receptor to the antibody that they're using to target. Basically, within a given indication, the products are limited to addressing those specific patients." The nanotechnology Sonrgy is developing is not dependent on a patient falling into these specific subcategories. "As long as we have detected the tumor and know where it is, we can point the ultrasound at it and deliver more drug independent of what proteins the cells may express on their surface."

A BIOTECH BY ANY OTHER NAME

Interestingly, Sonrgy calls itself a "preclinical biotechnology company" on its website. I ask Benchimol if that is more to avoid getting caught up in some of the pre-existing attitudes we mention above, and/or due to a lingering lack of larger recognition of nano as an important player in medicine. (How kind of me to provide him two negative choices.)

"Not really either," he says. "We have no problem calling ourselves a nanomedicine company. In fact, more to the point, I think nano is clearly becoming a subset of the greater biotechnology industry. So in that regard, yes, we are trying to make ourselves understandable to the broadest audience."

Sounds like a good strategy: Become one with the (perceived) opponent. Define yourself — correctly — as part of the solution to bring more and improved drugs and outcomes to patients. While I'm not qualified to know if this is an orthogonal application, it sure is another leveraging technique. And at the very beginning of this article we said Benchimol doesn't *yet* feel like a competitor to "conventional medicine." But if Sonrgy, and other nanomedicine companies on the rise, are successful, commercialization will have them going after some of the same markets as biotechs and pharma companies. In the spirit of this type of competition, and for the advancement of human health, let's hope they get the recognition they deserve and are ultimately successful in their pursuit of nanomedicine. L

Should Drug Repurposing Be A Part Of Your Strategic Plan?

ED MISETA Executive Editor @OutsourcedPharm

Cures Within Reach has been around since 1998, but the nonprofit, which started as a family foundation, did not become a public charity until 2005. The organization has primarily been funding medical research to accelerate the search for cures, but by 2010 its 190 de novo (new drug) projects had not touched the life of a single patient.

Ten other projects, which happened to be research on drug repurposing (finding a new indication for an existing medicine) had four successful outcomes, with medicines being used in clinics to save and improve lives.

"At that time, we realized no one else was really focused on drug repurposing, especially with generic drugs," says Dr. Bruce Bloom, president and chief science officer for Cures Within Reach. "We decided that should be our mission, and that is where our focus has been for the last five years. Since then, 50 of the projects we have funded have been proof-of-concept clinical trials for drug, medical device, and nutriceutical repurposing. Twelve therapies are either being used clinically or are in Phase 3 trials on their way to commercialization."

The benefits of repurposing an existing drug, especially a generic, are huge. Cures Within Reach will start with a drug that is known to be safe and effective in humans. That enables a significant amount of time and cost to be removed from the process. "Many of the hurdles you face with a new drug simply disappear," says Bloom. "Sometimes we are able to get a new repurposed therapy from ideation to patient use in three years or less, and for under $500,000. That is a substantial savings over the 10 to 20 years and $2 billion you might face for de novo research. Knowing the drug is already safe for use in humans can speed up both the IRB (institutional review board) and the FDA IND (investigational new drug) approvals."

"If there is a rare disease with no known cure, clear results from a robust clinical trial on a repurposed drug will often be enough to convince a physician the solution created is safe, inexpensive, and a good treatment option for their patient," says Bloom. "They also see the results in publications and talk to other physicians about it and then opt to prescribe it off-label to their patients."

For some indications, there may be a change in the drug that creates some commercialization value because it provides intellectual property protection. In those cases, Cures Within Reach will find a company to pick it up and move it through the regulatory pipeline. The organization's supported research has created several devices and compounds currently moving in that direction. Still, most of its efforts revolve around repurposing generic drugs. Because generics generally have multiple manufacturers, it can be easier to get donations of the drug for the clinical trial.

DRUG COSTS ARE A CONCERN

The cost to the healthcare system is always a concern whenever a new drug hits the market. Although new medicines will make patients healthier, they will almost always cause a significant increase in the cost of healthcare. When a repurposed drug comes out, it will also make patients healthier but will often decrease the cost of healthcare.

"In a lot of the rare diseases we have worked on, the patients were sick and there was no treatment option available," notes Bloom. "Some of those patients may have been hospitalized for significant portions of their lives, at a cost of up to $100,000 per year. With an effective repurposed drug, many of those other healthcare costs can

disappear, and the cost of caring for that patient might fall to maybe $5,000 per year. As a result, both the patient and the healthcare system benefit."

Bloom provides a couple examples of the benefits that can arise from repurposing. Cures Within Reach is hoping to start a global project with a number of industry and nonprofit partners in 2016. The goal is to determine whether Metformin, a Type-2 diabetes drug, can help patients with tuberculosis (TB). Metformin has been around for many years and is used by hundreds of millions of people around the world. It also seems to have an effect on the tuberculosis bacteria, making it more susceptible to antibiotics.

"Our study will add Metformin to the anti-infective protocol for TB," says Bloom. "Right now, TB is so drug resistant that patients have to take four medications simultaneously. For many patients, that combination still doesn't work. It appears adding Metformin to the mix might increase the number of patients benefiting from the treatment and also decrease the amount of time they have to take the drugs."

Another example is sildenafil (Viagra), which is now being tested as an anti-cancer treatment. Bloom notes tumor cells have numerous ways of escaping the body's immune system and continuing to grow out of control. For that reason, chemotherapy treatments will often destroy some, but not all, of the tumor. By adding sildenafil, which blocks one way cancer cells grow uncontrollably, to the treatment regimen, more of the standard chemo treatment is able to shrink the tumors.

FIRMS HAVE DIFFERENT GOALS

While pharma performs the drug discovery function well, attempting to repurpose a medicine is not always in their best interest. If a company has a blockbuster drug bringing in $2 billion per year treating diabetes in patients over the age of 45, that company would certainly want to protect its cash flow.

Even if the medication seems to hold promise as a cure for a rare or common pediatric disease, pursuing that indication can be risky. If a child were to get sick or die, or if it caused a growth disturbance in those children, the blockbuster drug will suddenly have a black mark on it. For that reason, pharma has to be very careful about what part of the life cycle they choose to go after when repurposing.

Pharma companies also have more good opportunities than they can often manage internally. For that reason, they will often outsource the repurposing. According to Bloom, they may opt to license that repurposing opportunity to a small biotech. The other company can absorb some of the financial and other risks while pro-

viding the pharma company with first refusal to relicense it back at a later date.

"As a not-for-profit organization, we are starting to get more requests from pharmaceutical companies for ideas to repurpose some of their end-of-life-cycle compounds," states Bloom. "By getting a method-of-use patent on a new disease indication, they might be able to extend the patent life of that drug, or at least their branded version of it. When a drug comes off patent, anyone can make it. But if you are the only company that can market it for the new disease indication, you may be able to maintain some of that market share."

NEITHER RESEARCHER NOR FUNDER

Cures Within Reach is not a venture capital firm. It does not invest in research, it does not develop molecules, and it does not conduct research. But its ability to get needed medicines to patients in need cannot be overestimated. Bloom would like companies to think of the organization as a facilitator. Most of the repurposing research takes place at an academic research partner, and the organization is neither the researcher nor the funder … it just brings together the key players.

The nonprofit will find projects and have them scientifically vetted to determine the chances of the project delivering the desired patient impact outcome. Then, Cures Within Reach locates the needed funding and brings all of the pieces together. If the group is working with a pharmaceutical company, that company may be the funder but will not be involved in the actual research. There is a fundamental value to that because being a nonprofit means the organization gets a really good deal from its research institution partners.

"If a large pharmaceutical company goes to an academic research institution to conduct a study, it might cost them $2.5 million," says Bloom. "We might be able to get that same project done for under $400,000. The reason is that these partner institutions do not charge us for many costs, including institutional overhead and investigator salaries. They will charge us a bare-bones price because it is generally their repurposing idea, and they want to prove that it can work for patients. If a principal investigator at an academic research institution comes up with the idea, we line up the funding for them, and they are excited about the possibility of having their idea help patients."

More than 90 percent of Cures research partners are in academia, with the rest being small biotech firms. All funding comes from pharma companies, family foundations, disease-specific nonprofits, and individual philanthropists. Bloom states the organization has never had to work with CROs but would be happy to do so under the right circumstances. Most projects do not have to go through regulatory approval, so the expertise of a CRO is generally not needed. He believes that situation may change going forward and would be interested in obtaining pro-bono support from large CROs.

MAKE RESEARCH A WIN-WIN

Pharma companies can benefit from repurposing research because Cures Within Reach has a new Web platform, CureAccelerator, that lists repurposing research ideas from around the world, most originated by researchers and clinicians who otherwise might have no contact with a pharmaceutical company. The CureAccelerator Web platform can provide protection for the project's intellectual property as the ideas are moved through to proof-of-concept clinical trials quickly and inexpensively.

Often, when repurposing a drug, it shows promise for a new disease indication but does not ultimately deliver the desired result. Even in those cases, it might provide a tremendous amount of new data about pathways and molecular mechanisms that allows the pharma company to create new approaches. Bloom cites Thalidomide as an example. Once its mechanism of action was understood, Celgene was able to take the drug with a nefarious past and use it as the backbone for a series of new medicines that are analogs of Thalidomide.

"Nobody but government or philanthropy is likely to fund the repurposing of a generic drug with no profit potential."

DR. BRUCE BLOOM
President and CSO, Cures Within Reach

"We may eventually find out that Metformin has an effect on TB but is not the ideal treatment for that indication," notes Bloom. "With that information, another company might attempt to tweak it a little and perhaps create a better product. Add IP protection to that effort, and they have the opportunity to generate revenue from it. Some physicians might opt to use Metformin while others opt for the new drug. In that instance, our attempts to repurpose can act as a launch pad for new and better ideas."

Cures Within Reach currently has no government support, but Bloom notes efforts are being made to start to work with the NIH. "They [the NIH] have invested time in looking at shelved pharmaceutical compounds to see if they can find new indications for them. We have been pushing hard for them to do the same thing for generic drugs. Nobody but government or philanthropy is likely to fund the repurposing of a generic drug with no profit potential. We believe governments need to do that so we can expand this repurposing revolution and drive more treatments more quickly to more patients." L

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The Business Benefits Of Revisiting Abandoned Therapies

GAIL DUTTON Contributing Writer @GailDutton

There is an adage in the oncology community that if the cancer doesn't kill the patient, the chemotherapy will. Serious side effects and the ability to develop more targeted therapies redirected oncology research from small molecules to immunotherapies, including immune system activators, checkpoint inhibitors, and CAR T-cells. Small molecules were largely forgotten.

DelMar Pharmaceuticals is helping to change that. Its small molecule oncology program began with a short list of compounds that advanced to Phase 2 at the NIH but were never commercialized. Those drugs had proven clinical activity and published data, which reduced the development risk. They were put on the shelf at the dawn of the genomics revolution, before the explosion of knowledge regarding tumor biology, underlying causes of disease, and mechanisms of action.

SMALL MOLECULES MAKE A COMEBACK

DelMar is focused on developing a treatment for glioblastoma (GBM), rare, malignant brain/spine tumors. Jeffrey Bacha, president and CEO of DelMar, says, "As the understanding of tumor biology evolved, it became clear there are different phenotypes [observable traits] driven by epigenetics [alterations to an organism caused by changes in gene expression] or drug resistance for which there is great unmet need."

DelMar researchers found that a leading anti-cancer drug, Temodar (temozolomide), was ineffective if the targeted tumor overexpressed the MGMT enzyme. Basically, it prevented apoptosis — the programmed cell death that would kill the tumor cell. "Our lead compound, VAL-083, is just different enough from temozolomide that it works against the type of GBM found in two-thirds of patients who don't respond to temozolomide and Avastin — an antivascular endothelial growth factor [VEGF] antibody used as a second-line treatment for recurrent GBM," Bacha explains.

LEVERAGING HISTORICAL DATA REDUCES RISK

By developing drugs that were in Phase 2 trials many years ago rather than creating entirely new drugs, DelMar has the benefit of beginning a program with a large body of knowledge. "If there was clinical activity then, there will be clinical activity today," he says. For example, safety and pharmacokinetic data from more than 1,000 patients using the original compound is in the National Cancer Institute's (NCI's) database. This reduces, but does not remove, developmental risk.

For example, with VAL-083, "The FDA raised concerns about the lack of safety data for patients exposed to VEGF inhibitors, which increase the risk of bleeding, and then to VAL-083, which depletes platelets," Bacha says. The question was whether, despite allowing Avastin to clear the system, its effects on the blood vessels would remain. "There was still a lot of work to do," Bacha says.

Also, while the old trials proved VAL-083 could be synthesized at scale, cGMP guidelines have changed in the 20 years since the drug was originally manufactured. For example, methods governing lot-to-lot variability have become more stringent.

Responding to those changes, however, also conferred benefits. "We had the opportunity to create new IP around the analytical methods to control variability and to detect the compound's unique fingerprint," Bacha says.

VAL-083 has orphan drug status in the U.S. for gliomas. This is possible because cancer is a subset of many divergent diseases, so each cancer is different. The types of cells from which tumors arise, their location in the patients' bodies, the mutations that direct their formations, and other

factors are all differentiators. "Gliomas, for example, are different from lung or breast cancer, even if those cancers eventually spread to the brain. Their treatments will be different, too."

Such differences dovetail with the emerging personalized medicine approach, which lets researchers identify patients unlikely to respond to the current standard of care. "It's well-known that overexpression of MGMT is correlated with poor outcomes, so we don't have to prove that correlation," Bacha says. "We don't even have to develop a companion diagnostic, because pathology reports already measure the expression levels of the MGMT enzyme."

PRIOR CHINESE APPROVAL WAS A SURPRISE

In a serendipitous twist, VAL-083 already is approved in China. DelMar didn't realize that until it began searching for a CMO. When conducting due diligence, the company searched for new patent filings that would establish a modern IP position related to its compound. The older filing in China, therefore, wasn't evident.

"We learned of a very good CMO in China that already was licensed by the Chinese FDA to manufacture this compound for chronic myeloid leukemia [CML] and lung cancer. That compound was an older drug, even in China, so there were concerns about the drug and the manufacturing process," Bacha recalls. DelMar developed analytical methods and tested the Chinese version of the compound to modern standards, eventually using that compound (produced under DelMar's specifications and labeling) for clinical trials in the U.S. "That saved us a lot of time and money."

That approval didn't add immediately to the market, however. The manufacturer, Guangxi Wuzhou Pharmaceuticals, has the marketing rights in China for the older version of this compound for CML and lung cancer but had put very little effort into marketing the drug. DelMar's new patents modernize the drug and should support sales growth under Guangxi's current approval in China as well as for global approvals.

DelMar is working with Guangxi to determine how to jointly commercialize the product in China. "Guangxi could license rights to a company with an established oncology sales force in China, or it could establish a new sales force itself. In fact, it has very successfully built a new sales force for cardiovascular products," Bacha says. Either way, it is the new data being developed by DelMar that will drive the global opportunity for new treatments and sales revenue with VAL-083.

Bacha says most Chinese physicians DelMar surveyed had never heard of the compound. Those who had heard of it were unsure where it fit into a treatment regimen that included platinum-based chemotherapy or tyrosine kinase inhibitors. DelMar's preclinical work with researchers at the M.D. Anderson Cancer Center and the British Columbia Cancer Agency shows that VAL-083 has synergies with platinum-based therapies without overlapping toxicities and is active in tumors resistant to platinum-based chemotherapy regimens.

"NCI data shows a fair breadth of activity in multiple cancers, including nonsmall cell lung cancer," Bacha says. "Our drug may have a niche in combatting solid tumors for patients whose cancer is resistant to treatment due to p53 mutations. That includes lung, ovarian, and cervical cancers. This would fill a big need."

VAL-083 is in Phase 2 clinical trials at five U.S. sites, and DelMar plans to initiate a new postmarket Phase 4 trial for lung cancer in Shanghai in 2016.

A PARADIGM SHIFT IN CANCER THERAPY?

Bacha says VAL-083 could cause a paradigm shift in cancer therapy. Despite the enormous advances in cancer treatments during the past 20 years, very few applied to glioma. Median survival rates have not improved.

"At the 2011 meeting of the American Society of Clinical Oncology, physicians said they wished they had a new therapy that crossed the brain barrier and lacked MGMT-related resistance problems. That's what our drug does," Bacha says.

VAL-083 is relatively well-tolerated compared to other chemotherapies. The average life expectancy of patients entering one of DelMar's trials is three months. The company's data suggests that with VAL-083, median survival is nine months after only one to two cycles of therapy. Bacha says he expects the compound to allow much longer life expectancies for patients in the early stages of disease.

TWO-PRONGED COMMERCIALIZATION STRATEGY PLANNED

DelMar is planning a bifurcated commercialization strategy for academic medical centers and community oncologists. Patients treated today for refractory glioma tend to be treated in a few large academic medical centers that typically run Phase 2 and Phase 3 trials. "With only 69 NCI-designated cancer centers, we could market to them ourselves," Bacha says.

Newly diagnosed glioma, lung, and breast cancer patients, however, tend to be treated by community oncologists. Their numbers are significantly larger. "The infrastructure required to serve this market is far beyond our scope today so, ideally, we would partner with a Big Pharma company that already has a strong foundation in place to reach community oncologists," he says.

EXPLOIT SYNERGIES WITH IMMUNOTHERAPY

"Chemotherapy and immunotherapy go hand in hand," Bacha says. "Both create an opportunity for added benefit in combinations."

DelMar is watching advancements at immunotherapy developers to see which are most likely to be approved. As they advance, the company is considering which combinations would be most interesting. For example, there's great anticipation surrounding Celldex Therapeutics rindopepimut. "Rindo may be the first new drug approved for GBM in many years that meaningfully improves survival," Bacha says. That's obviously good for patients, but it may be good for DelMar, too; the company would consider combinations or collaborations with any valuable immunotherapy.

Twenty years ago, the biotech revolution was just beginning. Many potentially viable compounds were shelved then because of problems that now can be resolved. DelMar's experience with VAL-083 shows it's possible to develop robust IP to make previously overlooked drugs commercially viable.

"By reinvigorating overlooked compounds, there are wonderful opportunities to benefit patients," Bacha says. "The value of the modern understanding of tumor biology and mechanisms of action can't be overstated. There are huge opportunities." L

Building An Entrepreneurial Health Sciences Ecosystem From The Ground Up

FRED OLDS Contributing Writer

There is an opportunity loss in the research dollars funded by the NIH, says Atul Varadhachary, M.D., Ph.D., managing partner of Fannin Innovation Studio. He says about 16 percent of NIH research funding goes to San Francisco and Boston, yet those regions capture about 85 percent of venture-backed commercialization.

"Clearly the two VC-dominant regions import some technology from elsewhere in the U.S. Even if you adjust for that, the return on the 84 percent of NIH tax dollars funding research between the coasts is still extremely low," says Varadhachary. "The research just dies without being translated into products that improve our lives and make money for investors." He says what's missing in the heartland is the experienced, integrated ecosystem with its capacity to form companies, finance development, and carry out value-creating translational research.

Fannin has developed a plan to capitalize on the opportunity. Fannin Innovation Studio is an early-stage life sciences company in Houston focused on commercializing innovations developed in the Texas Medical Center Institutions. With two medical schools, major universities and hospitals, and M.D. Anderson Cancer Center, finding and conducting innovative research in Houston is not an issue. The number one challenge is finding health science managers to guide translational research. "In a sense," says Varadhachary, "in the classic VC model found in Boston and Southern California, VCs don't fund research; they fund management teams. In places like Houston, those management teams don't exist." With so much opportunity and so few entrepreneurs, Fannin had to develop an alternative commercialization model which allowed them to manage more projects and cultivate a community of health science entrepreneurs in Houston.

THE CLASSIC VC MODEL

Venture capitalists found Boston and Southern California to be fecund regions of innovative science and experienced leadership. Those areas were the birthplaces of high-tech and possessed a strong entrepreneurial spirit. There was a concentration of universities and health sciences institutions conducting novel research, and nearby major pharma and biotech companies developed life science business leaders. VCs bought or licensed the science from innovators and hired leadership spun off from pharma, and fledgling companies were born. It is a time-proven and effective model.

The classic VC model establishes an R&D plan toward an exit. Optimistically the exit is a sale to pharma, but criteria are also established for an exit with project termination. It requires large amounts of money to staff and operate stand-alone brick-and-mortar startups. Repetitive funding is crucial, and ownership can become highly diluted through the sale of additional shares to support continuing research. "In a system that can burn $500,000 a year, even at the earliest stages, speed to exit is critical," says Varadhachary. "So there is little room to explore secondary indications."

BUILD A MORE EFFICIENT SYSTEM

The Fannin model is built on partnerships. The company partners with innovators and their institutions (usually universities) to co-found companies to manage and develop the researchers' discoveries. There are four main components to the model: a single-pooled management team, innovative research, funding primarily through grants, and an entrepreneur development program.

Fannin uses a pooled team of experienced professionals to manage all of its portfolio companies simultaneously. This differs from the classic VC model which establishes startups in stand-alone offices for each company. "You need those early-stage life science entrepreneurs, but you don't need a single dedicated team for each individual project early on," says Varadhachary. "The analogy I like to use is nine women can't make a baby in one month. The process takes as long as the

process is going to take. More managers earlier won't speed the process."

There is no physical plant with a Fannin partnership. All parties work in their current locations, so there is no additional overhead. "In our model, the companies actually have zero-dollar burn rates in the first two years," says Varadhachary.

Partnership roles are clearly defined between Fannin and researchers. Investigators focus primarily on their research, but stay actively engaged with the commercialization. Fannin management provides funding and administrative and legal support, but Fannin's most critical role is providing direction to guide the research to commercialization. This is based on industry needs, market intelligence, and regulatory provisions.

IDENTIFYING INNOVATIVE RESEARCH

The company searches for innovative research that may be nine to 10 years from Phase 3 trials or commercialization. That far ahead, there is no way to predict the state of medicine, reimbursement, or competition, nor what the FDA will require. To deal with these vagaries, Fannin uses three criteria to select research: it must be paradigm-changing, it must offer optionality for more than one indication, and there must be a good fit between Fannin and the researcher.

Research meeting those criteria is reviewed to determine if it is based on good science and backed by grants and peer-reviewed publications. Then a vetting process assesses commercial potential, patentability, and whether a health sciences company would find it attractive.

Partnerships routinely monitor their company's innovation to make go/no-go decisions. At every stage of development they ask, "What tests can we conduct to disprove the hypothesis?" If for any reason the project doesn't appear headed toward commercialization success, it is shut down. It is an agnostic decision. No one loses a job. Very little investor capital is lost. The scientist finds out the research cannot be commercialized and focuses attention elsewhere. Fannin reassigns staff to other projects.

The decision isn't always go/no-go. Varadhachary says, "If the science still needs time to develop, we just turn down the burn on that company and let the science develop before deciding whether to accelerate or terminate. Our pooled management team model makes it easy to go into holding, and retain optionality."

USE CAPITAL EFFICIENTLY

A major departure from the classic VC model is that Fannin relies largely on grants from the NIH, Small Business Administration, and other sources. It does have some private investor capital, which it uses primarily as seed money or additional funding at critical stages of research. Grant funding increases efficiency because it reduces investor dilution, allows the partnership to investigate more than one indication, and reduces concerns about investor interference.

As an example, Pulmotect is a portfolio company that has received more than $19 million in funding. Its lead product is in Phase 1 human studies and has met important milestones. Just a little more than $1 million of that came from direct investor backing. The dilution to the original owners, including the inventors and their institutions, is much less than it would have been in a typical VC-backed enterprise.

Relying on grants, however, can lengthen the development process due to the application approval time line. So this model is not suitable when speed or large amounts of capital are required. Varadhachary says, "In our industry, speed to market is less important than capital efficiency. The cost, risk, and failure rates are so high that it's important to try to get more shots on goal for every dollar invested." He believes with the efficiencies of this model, Fannin can advance up to five times more compounds than the classic VC model with the same capital.

CREATE A SELF-SEEDING AND SUSTAINABLE ENTREPRENEURIAL ECOSYSTEM

One of Fannin's major goals is to create a Houston-wide entrepreneurial ecosystem of research and commercialization. This is not an altruistic endeavor. Varadhachary welcomes competition. Competition means more translational research, more commercialization, and eventually a reputation that attracts more entrepreneurs and the interest of industry. That, says Varadhachary, is good for everyone.

The biggest challenge in this endeavor is attracting and developing managers with expertise in life sciences. There are 4,000 to 5,000 students at the medical schools and centers in Houston, but the concept of starting a business is usually foreign to them. Yet, says Varadhachary, there is a growing fraction that is attracted by the opportunity.

"In our model, the companies actually have zero-dollar burn rates in the first two years."

ATUL VARADHACHARY, M.D., PH.D.
Managing Partner, Fannin Innovation Studio

As a core part of its business model, Fannin offers an apprenticeship to select health science professionals. "These people are very bright. They all have an M.D. or Ph.D. degree or both," says Varadhachary. The program allows them to work in a portfolio company one to two days a week for up to six months. During the program they are exposed to the entire Fannin portfolio, so they get a broad view of entrepreneurial operations.

The goal is to create a self-sustaining entrepreneurial community in Houston by seeding it with individuals who have gone through the program. More than 65 professionals have interned with Fannin in the last five years. As planned, most return to the medical community, with seven running their own biotechs in Houston, but nine continue to work with Fannin or one of its portfolio companies.

Fannin has started about 25 companies in the last seven years, with 12 still active today. It expects to create another 10 or 12 partnerships in the next three years.

"What we end up with is a process that's not driven by money because it's not driven by venture capital. It's driven by science, and we can take the appropriate time needed for the science," says Varadhachary.

Tax Considerations When Forming A Biotech Company

MARK SIMPSON, CPA, CFP, MBA

When a biopharmaceutical company is first being formed there are many important decisions to be made. For example, what type of entity should it be — corporation, partnership, an LLC? What should be the accounting method — cash, accrual, or some type of hybrid? You may be thinking about simply outsourcing some of these legal and accounting decisions.

After all, you are a busy biopharma executive, and your efforts should be focused on securing funds. Right? But during your company's early years, you know how important it is to stretch investment dollars. So don't give away part of your hard-won financing by failing to understand a few startup accounting basics.

From an accounting standpoint, during the first year of filing your biopharmaceutical company's taxes, many business decisions, once made, are irreversible. While it should go without saying that you should take great care in preparing and submitting your first tax return in a timely manner, one particular startup issue you should not lose sight of is the federal tax accounting treatment of organizational and startup costs.

PAY ATTENTION TO ORGANIZATIONAL AND STARTUP COSTS

Organizational costs are expenses incurred in forming a business entity, such as legal fees, state filing fees, and organization meetings (travel, facilities, etc.). Once formed, costs incurred prior to the "grand opening" are considered startup costs and include rent, utilities, and payroll. For tax purposes, both categories of costs must be capitalized and amortized over 180 months once the business starts operations. Both types of costs are treated the same from an accounting standpoint. Under the current tax law, the entity may deduct up to the first $5,000 of costs incurred, with the balance amortized straight-line (i.e., evenly) over 180 months. However, the $5,000 immediate write-off is reduced dollar for dollar as the total organizational (or startup) costs exceed $50,000. All costs will eventually be deducted for tax purposes. However, it may take 15 years to eventually deduct the expenses. Why is this important? Let's consider the startup costs examples (i.e., $45,000, $52,000, and $60,000) found in figure 1 to illustrate what a difference $15,000 (the difference between incurring $45,000 and $60,000 of costs) can make to your bottom line.

Not every CEO is an accounting whiz, and that's okay. However, don't let your lack of training in this discipline prevent you from realizing financial success. To help you maximize tax deductions, here are three key questions you must consider.

1 What costs are excluded based on the tax definition of organizational costs and startup costs?

Organizational Costs — Exclude costs incurred to issue securities such as syndication costs, brokerage commissions, and security printing costs. These costs remain on the tax balance sheet and are not currently deductible or amortizable.

Startup Costs – Exclude interest expense, real estate taxes, and R&D costs which are deductible as incurred/paid.

2 How is the election made to amortize the organization costs and startup costs?

For both startup costs and organizational costs, the election to amortize is automatic. No form or statement needs to be submitted. A taxpayer files the return, capitalizes the costs, and begins amortization on the initial tax return during which the business operations start (keep reading to see what year that actually is). There are a few technicalities to pay attention to. First, to be amortized, regardless of the accounting method used, the costs must be incurred by the end of the first tax year. Special planning needs to be taken for entities formed toward the end of the first tax year.

FIGURE 1

	EXAMPLE 1	EXAMPLE 2	EXAMPLE 3
Startup costs incurred	$45,000	$52,000	$60,000
Phase-out starting point	$50,000	$50,000	$50,000
Lost write-off	$2,000	$10,000	–
Maximum write-off	$5,000	$5,000	$5,000
First-year write-off	$5,000	$3,000	–
Amortizable amount	$40,000	$49,000	$60,000
Amortization period	180	180	180
Monthly amortization	$222.22	$222.22	$222.22
Number of months in the first year	12	12	12
Amortization expense	$2,666.67	$2,666.67	$2,666.67
Total first-year startup expense	**$7,667**	**$6,267**	**$4,000**

For example, if you finally get your funding in late October and are thinking of starting your company in December of that year (with a 12/31 year end), be sure to act quickly and have all of the legal documents completed before year end. If, for example, the organizational minutes are overlooked and legal counsel drafts the documents in January of the second year, these organizational costs must be capitalized and remain on the balance sheet and are not amortizable. No tax deduction will be allowed for the legal bill since not incurred in the first year. Second, once made, the election is irrevocable. If amortization is "forgotten" in the first operational year, your business, in essence, made an election to not deduct the startup amortization expense. Such a decision cannot be reversed or corrected by filing an amended return!

3 When does an active trade or business actually start?

Unfortunately, that is the million-dollar question to which we have nothing but subjective guidance. District courts, U.S. tax court, IRS letter rulings, and IRS revenue rulings reach different conclusions. The core issue is determining when an entity becomes a "going concern" (i.e., fulfilling the business purpose for which it was formed).

For example, in a 1965 circuit court case, a company formed in 1952 to operate a television station was held to have a four-year startup period. How was this determined? Well, the company did not begin broadcasting until 1956. The key determining factor was the year that company obtained its license, followed by when it began performing services for which it had been organized. Without the proper license, the broadcast company could never be a going concern. A similar conclusion was reached in an IRS technical advice memorandum ruling an electric utility company began operations when it began generating electricity.

A 1990 IRS letter ruling determined a manufacturing company began operations when its manufacturing equipment met quality standards, and it could begin production. In a 2009 case, a real estate business created to rent, buy, or sell property did not begin operations until the first piece of real estate was purchased. Expenses incurred prior to the first closing were held to be startup expenses.

The bottom line is, based on the various holdings, a business begins when (1) assets are ready, even though no income has been generated, or (2) when assets are ready and revenue is being generated.

DEFINE YOUR COMPANY'S PURPOSE

When you are faced with a lack of clarity, perhaps the key consideration to focus on is being sure to properly define the purpose of the business entity. If a business is created to develop, test, and manufacture a new drug, the IRS could take the position that operations do not begin until the drug is being produced and sold or perhaps, ready for production. This could result in many years — a decade perhaps — of startup costs. During this time period, time grants and other sources of income may have to be recognized. If you don't have appropriate offsetting expenses, this can result in having an unnecessary taxable income. If, however, the process was broken up, such as one company being tasked with researching the potential drug, the startup period would be minimal, ending once the initial research begins. The research company would have normal, ordinary, and necessary business expenses that could be deductible, thereby offsetting various sources of income or creating net operating losses that could be carried forward until grants or milestone revenue is recognized.

So, what does all of this mean to a biopharmaceutical startup whose precious dollars should be put to good use instead of being turned over to the government by paying unnecessary taxes? The mechanics of the organizational tax deduction are relatively simple. Namely, you need to carefully plan the activities so all costs are incurred in the first year, and then you can actually begin to deduct the amortization in the first tax year. From a startup cost vantage point, the mechanics are the same. However, the critical startup period will be defined by the business purpose of the entity, and much care should be given to developing such a purpose. A narrowly focused business purpose could result in a few-month startup period resulting in more currently deducted operating expenses (i.e., research, manufacture, or product distribution). A broad business purpose could result in years of capitalized costs deducted slowly over 15 years.

As with any tax strategy, always check with your tax advisor to ensure decisions are made based on current tax law and guidance issued by the court system. L

Mark Simpson is the controller of VertMarkets Inc. and a professor at Mercyhurst University Walker College of Business..

Should Your Executives Help You Recruit?

MORTEN NIELSEN

Morten Nielsen is the global managing director, Global Life Sciences Practice, for the executive search firm Witt/Kieffer. He can be reached at mnielsen@wittkieffer.com or at 609-558-7714.

No industry is more competitive than the life sciences for leadership talent. And we all know there are obvious advantages to asking one's own leaders to help recruit, but allow me to offer a few words of caution if this is your strategy. There are several issues at stake that require forethought:

- **Conflicts of interest.** Whenever an executive recommends someone from his or her network for a position, there could be a tacit belief that the candidate will be given not just fair but special treatment. There may also be the presumption that the recommended party will be the candidate of choice, perhaps the only candidate under serious consideration. In some cases this may be true, but most often it is not. Whenever executives are asked to help recruit, extra measures must be taken to make explicit that there will be no favoritism given to recommended candidates, and that each applicant will undergo the same rigorous interviewing and vetting process as all others. Otherwise, it is a recipe for confusion and hard feelings.

- **Fairness.** When recruiting for any position it is important to give fair consideration to any and all interested candidates, especially those not recommended by someone inside your organization. Looking at the other side of the coin, a fair and open search is critical for whomever is hired, particularly a referred candidate. It can be extremely difficult for a newly hired executive to establish credibility with colleagues and subordinates if there is a whiff of suggestion that he or she was inserted into the role without proper vetting. A company does no favor to an executive by hiring that person through a hasty or incomplete process.

- **Confidentiality.** More than ever, expert recruiting requires utmost confidentiality, as rumors or information leaks during a search can jeopardize not only the recruitment itself but also the careers of the executives involved and the reputation of one's firm. Professional recruiters, whether internal or retained, have concern for privacy in their DNA. They well understand the risks involved and make it standard practice to protect candidates and the veracity of the search process as much as is possible. When executives become involved in recruiting, it becomes much harder to maintain confidentiality.

- **Finding the Best Talent.** Asking your executives to suggest potential candidates may bias a firm towards recommended candidates. It may also come at the expense of conducting a comprehensive search for the best person available. It is tempting to have a viable candidate presented on a silver platter and to jump at the chance. The inclination is to fill the position—"Let's get someone in here who can do the job, and fast." Those two goals aren't always compatible. Getting the right person, for the right job, for your organization is best done through a thorough, deliberate process. Good recruiting can be done quickly, but pace should not be the only selection criteria.

RULES OF THUMB

What does the organization owe its executives who recommend candidates? Honesty and transparency. In my mind, there are a few simple guidelines to follow:

1. **Ask but don't promise.** By all means, solicit candidate referrals from executives and staff. Then make no promises other than that recommended candidates will be fairly considered and treated.

2. **Communicate.** Keep recommenders apprised of the progress of a search. This doesn't mean giving them inside information on the status of the recruitment, but letting them know what stage the search is in and whether or not their suggested candidate is still under consideration.

3. **Say thank you.** When the hiring process is complete, express appreciation to recommenders regardless of the outcome. They have gone out of their way to try to help the firm.

The war for talent in the life sciences is real. It makes sense for a firm to ask its executives to help win the war, as long as there are clear rules of engagement. L

Strategic Financing Alternatives For Later-Stage Companies

MICHAEL O'DONNELL

Michael O'Donnell is a partner in Morrison Foerster's Palo Alto office, specializing in corporate and securities law. He has more than 30 years of experience providing general corporate representation to biopharma and other life sciences companies.

With the exception of several mega-financings for blue chip management teams in companies such as Juno and Denali from syndicates of well-heeled venture funds such as ARCH Ventures and Flagship Ventures, venture financing for startup life science companies has been relatively lean for the last several years. However, the good times were rolling in 2014 and early 2015 for later-stage biopharmaceutical companies with a substantial number of IPOs, which in turn led to a significant increase in the number of mezzanine financings, representing easy money for later-stage biopharma companies. Mezzanine financings are intended to be the last financing round prior to the IPO with investments being made by so-called crossover investors such as RA Capital and Deerfield, which participate in both private and public financings. Mezzanine financings are attractive to companies because they can be completed faster and more easily than an IPO without the necessity of public disclosure of company information, and they provide the company with a group of new investors who are likely to participate in the company's IPO, priming the pump for successful marketing of the IPO to follow. Mezzanine financings are attractive to the crossover investors because they enable the investor to invest at a discount to the IPO price and provide the investors with a high degree of assurance that they will be able to fully participate in the IPO syndicate when they might otherwise be shut out of a hot offering.

When things go according to plan with the mezzanine financing followed by a well executed IPO, it is a win-win for the company and the investor. IPOs with crossover investors have performed better than IPOs without crossover investors. However, if the IPO window begins sliding shut (as has happened recently) following the mezzanine investment, the company is stuck with impatient investors desiring liquidity, which can lead to tension between management and the investors due to divergent interests. As would be expected, the recent tightening of the IPO market, with deals getting smaller and being done (if at all) at lower valuations, has had a severe impact on the current availability of mezzanine financing.

So what's a later-stage biopharma company (BioCo) to do? One alternative that has been used by a number of my clients is an option deal with a Big Pharma company (PharmCo) which is interested in acquiring BioCo or rights to a particular BioCo product but wants to see more progress before actually doing so. In exchange for a large (say $50-$75 million) up-front cash payment, PharmCo is granted the right for a period of time (usually until the achievement of a specified clinical milestone) to acquire BioCo or exclusive rights to the product on pre-agreed terms including the purchase price. Note that the up-front cash payment can be structured either as an option fee, which is better for BioCo but will have adverse accounting treatment for PharmCo, or as an equity investment at a price favorable to BioCo, which will involve dilution for BioCo shareholders but may enable more favorable accounting treatment for PharmCo. Also note the option may be structured as a "put" where PharmCo must exercise the option if the specified milestone is met (which is better for BioCo but may lead to a considerable amount of negotiation over what exactly it means to meet the milestone), or a "call" where PharmCo can elect to exercise the option whether or not the milestone is met, which is simpler to implement.

Once again, when things go according to plan, the option deal structure can result in a win-win. BioCo can raise the cash necessary to achieve the clinical endpoint enabling a successful sale of the company or the product rights while PharmCo can mitigate the risk that the milestone may not be met. But there is the rub for BioCo. If PharmCo does not exercise the option, BioCo is left at the altar with a program perceived to be a failure and therefore difficult to further finance or sell to someone else. To avoid that problem, BioCo needs to raise enough cash in the initial option payment to not only fund all development costs to achieve the milestone but also to fund all of its operating expenses for at least 12 months, but ideally 18 months, after the expected date of the milestone completion. In doing so, BioCo will have enough time for the taint of PharmCo's decision not to exercise the option to wear off and allow BioCo time to come up with plan B.

The changing winds of mezzanine financing require later-stage biopharmaceutical companies to constantly seek creative alternative financing structures. Option deals can provide companies with the cash necessary to obtain sufficient clinical data to raise additional private or public equity financing or achieve liquidity for the company's shareholders.

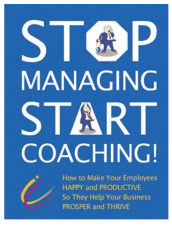
Stop Managing!

Start Coaching To Increase Productivity And Profitability

DR. TERRI LEVINE

Dr. Terri Levine is a best-selling author and was named one of the top-10 coaching gurus in the world and top female coach in the world. She is a leadership mentor to companies worldwide. Contact her at Terri@TodaysCoaching.com.

terrilevine.com



Management is dead and doesn't work. As you move into a coaching-based leadership model, a main area of coaching focus will be teamwork. Teamwork is the art of having a group of people work together harmoniously and effectively toward a goal or with a particular purpose. It is that unique melding of group work and individual personality into a well-functioning unit. It includes the one-shot, all-important push toward a specific performance target and/or the day-to-day operations of a business unit.

By coaching teamwork you can help your employees function better. By coaching individual employees to improve their performance, you naturally will help produce better teamwork among those who report to a specific supervisor. In any case where teamwork is an issue, the coaching goal is for the team, the team leader, or both to become more thoughtful about how the team works together and to turn that thoughtfulness into activity that will produce a team that willingly works together to create extremely high performance.

The following coaching questions are intended to create that thoughtfulness. These questions and the corresponding answers are the foundation for effective coaching around teamwork. Your further work with a team will build from what the team leader and the team members — if involved in the coaching process — tell you. So, as with all other coaching, your first job is to be fully present with, and responsive to, the team.

These coaching questions will open the door. Use your wisdom and understanding of the team and situation to expand upon this list.

TOP QUESTIONS FOR COACHING TEAMWORK

1. **Is the team challenged on a regular basis?**
Real teamwork is created out of meaningful goals and projects that challenge a team. It is therefore important for the team and the team leader to identify what work would be significant both for the business and the team and to use that work to build the team.

2. **Is the team a manageable size?**
Teams that are too large are unmanageable. Teams that are too small lack the synergy and energy necessary to grow and thrive. The leader and team should be able to quantify the minimum and maximum numbers of members necessary to work well and without struggle.

3. **Has the team developed a common purpose?**
Teamwork comes more naturally when the team has a common purpose. The purpose may involve a specific type of work for the business. It is important that the team contribute to developing the common purpose so that each member owns that purpose. If the common purpose is dictated strictly from above, it is often difficult for members to adopt and accept it as their own.

4. **Does the team have measureable goals?**
Teamwork accelerates when there are specific measurables that tell the team how they are performing. Again, it is important that the team have significant input into development of the measurables if the members are to feel fully accountable for achieving those metrics. L

Your Process is only as Smart as its Parts.

Developing a high cell density or continuous process is not easy. Single-use technologies add flexibility, but how expandable is your hardware and software? Most systems make it difficult to add pumps, sensors and ancillaries after the fact which often leads to inefficient workarounds.

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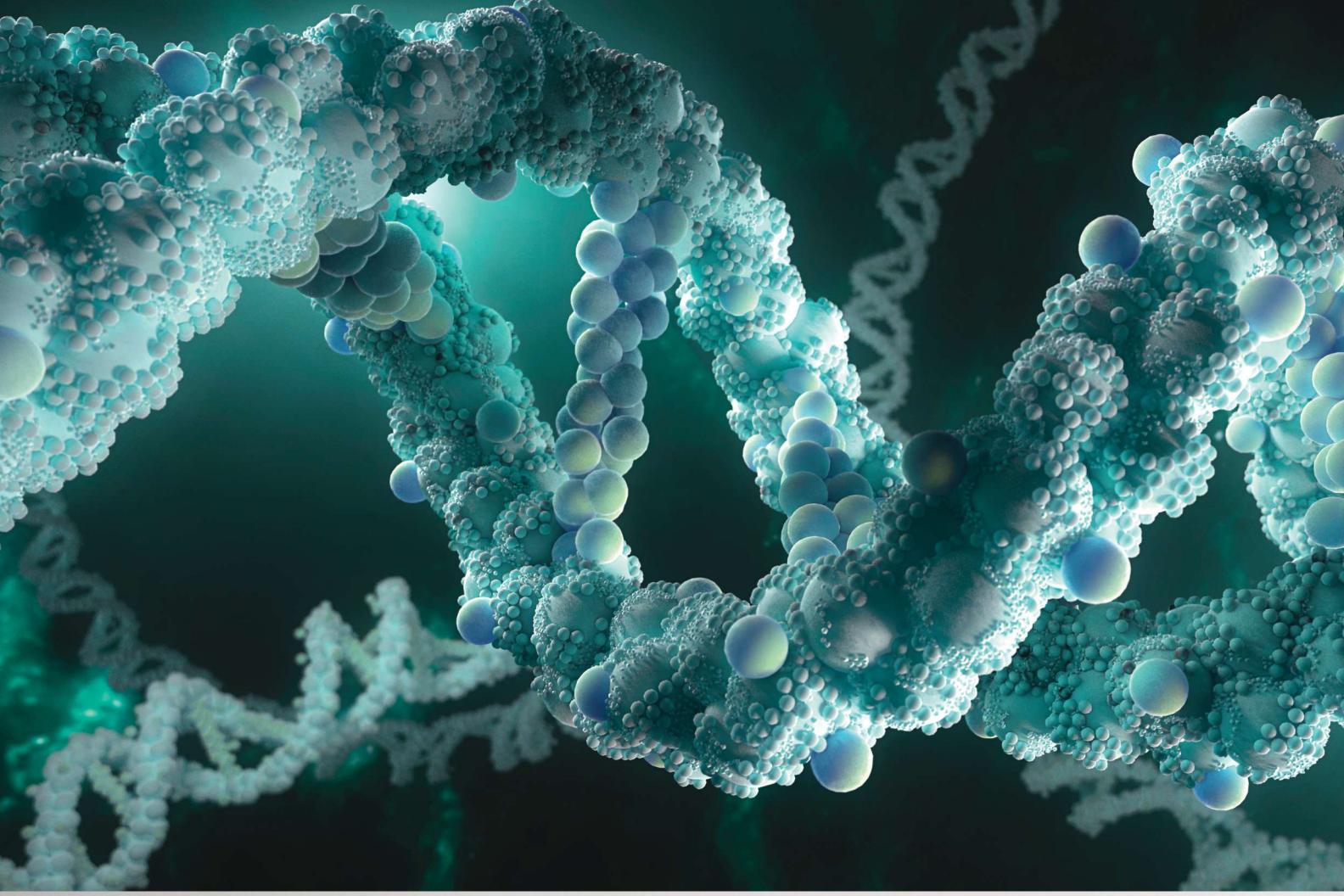
- Pumps that can be recognized with drop down menus
- Gas Manifolds that are “hot-pluggable” and auto-detected by our software
- Bioreactors that are easily exchanged and configured



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