Life Science Leader

Connect. Collaborate. Contribute.

SEPTEMBER 2017

Behind The Scenes Of Allergan's Social Contract

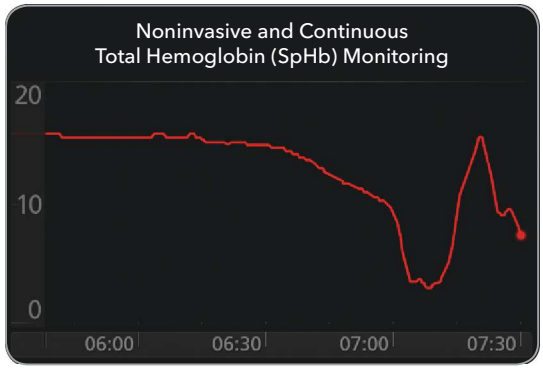
p. 16

Brent Saunders, chairman, president, and CEO, Allergan

For transfusion decisions made in real-time, don't you need real-time data?

SpHb noninvasively provides continuous visibility to changes in hemoglobin, which may help clinicians make more informed and timely transfusion decisions.

Peer-reviewed studies have found that using noninvasive SpHb monitoring in conjunction with invasive blood samples has helped clinicians to:



Reduce Unnecessary Transfusions

in low blood-loss surgery:

- > 87% reduction in transfusion frequency (from 4.5% to 0.6%)[1]
- > 90% reduction in average units transfused (from 0.1 to 0.01 units per patient)[1]

in high blood-loss surgery:

- > Reduction in the percentage of patients receiving 3 or more units from 73% to 32%
- > 47% reduction in average units transfused (1.9 to 1.0)[2]

Initiate Timely Transfusion When Transfusions Are Needed

in high blood-loss surgery:

- > Transfused an average of 41 minutes sooner[2]

NOW Available in Philips Monitors

PHILIPS

For more information, visit

www.masimo.com

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information, including indications, contraindications, warnings, and precautions.

Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering among other factors: patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples. SpHb monitoring is not intended to replace laboratory blood testing. Blood samples should be analyzed by laboratory instruments prior to clinical decision making.

[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9.

[2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4.

Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyzer.

PLCO-001129/PLMM-10560A-0717
PLLT-10328A


Pfizer CentreOne
Contract Manufacturing
When it's
YOUR
compound,
every step
matters.
www.pfizercentreone.com
API
STERILE INJECTABLES
HIGHLY POTENT SOLIDS
PC1-16-0005/R2-8.125x10.875in © 2016 Pfizer Inc. All rights reserved. Pfizer CentreOne is a Trademark of Pfizer Inc.

CONTENTS

Welcome to

Life Science Leader

SEPTEMBER 2017 VOL. 9 NO. 9

@LifeSciLeader1 linkedin.com/company/life-science-leader facebook.com/LifeScienceLeader WWW.LIFESCIENCELEADER.COM

LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 9, No. 9 is published monthly by Jameson Publishing, Inc. at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5587. Periodical postage paid at Erie, PA 16510 and additional mailing offices. **SUBSCRIPTION RATES** For U.S. based subscribers, $295 for one year. If your mailing address is outside the U.S. the subscription price is $445 for one year. **POSTMASTER:** Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. **PUBLICATIONS AGREEMENT:** No. 40722524 c/o AIM, 7289 Torbram Road, Mississauga, ON L4T 1G8.

When you
think equipment,
think **Federal Equipment**

PHARMA
CHEMICAL
PLASTICS/ RUBBER
PACKAGING
FOOD & BEVERAGE
TRAINING
UTILITIES

THINK SHORTER LEAD TIME

Federal Equipment Company has on-hand inventory in more than 200 categories, enabling you to source reliable processing and packaging equipment that's housed in clean, climate-controlled warehouses. We obtain much of our inventory by providing asset management programs to large, multinational companies. This gives you a wide range of options to get the leading OEM-brand equipment you need from reputable sources installed and operating in your facility as fast as possible. No matter what your equipment needs are, make Federal Equipment your first call.

Visit us at

Pack Expo / Healthcare Expo, Booth # 345
Las Vegas, NV, September 25 - 27, 2017

SupplySide West, Booth # ii146
Las Vegas, NV, September 27 – 28, 2017

+1 877 536 1509 > www.fedequip.com

Federal Equipment Company

Life, Liberty, And The **Pursuit Of Healthiness**

ROB WRIGHT Chief Editor

A little over two years ago, my wife's employer informed her that, if I was able to get health insurance through my employer, I would have to do so. We had always kept the family on one health insurance policy, as this seemed easier for managing prescriptions, and so on, but now she and the kids are on one plan and I on another. We didn't think much about the change until my wife went to pick up a prescription for me in January 2016. On her plan, the medication I had been taking for at least 10 years was a $20 copay. But when she went to pay for the medicine on my new plan, she was informed the copay would be a little under $900 — for a generic drug. Not surprisingly, that medication was left at the pharmacy counter, because with two kids in college, a 4,400 percent increase (i.e., $240/year to $10,800/year) wouldn't be easily absorbed in the family budget. But don't worry; we worked with my doctor to find a suitable and affordable replacement.

Of course, my family is not alone in such healthcare/drug price increases. A few months prior to my experience, patients — and, it seems, society in general — expressed outrage when Martin Shkreli implemented his 5,000 percent increase of Daraprim. The public's clamor continued as Heather Bresch, the CEO of Mylan, jacked up the price of her company's popular EpiPen by 400 percent. Suddenly high drug prices and "evil" pharmaceutical companies became synonymous, which created enticing political fodder for presidential candidates Hillary Clinton and Donald Trump. And while many biopharmaceutical CEOs publically chastised such drug-price-increase behavior, one CEO took a very different approach.

On September 6, 2016, Brent Saunders, chairman, president, and CEO of Allergan, published his CEO Blog "Our Social Contract with Patients" — a set of drug pricing rules for Allergan to live by. In the blog, Saunders notes how "the healthcare industry has had a long-standing unwritten social contract with patients, physicians, policy makers, and the public at large." It is understood that making new medicines requires significant investment, and companies taking on such risk have to price medicines so they are accessible to patients, while also providing sufficient profit to encourage future investment. "It was designed to be a win-win-win," he wrote.

The concept of a social contract is not new; social contract theory is an old philosophy establishing moral and political rules for how rational people in a society should live together. So why did Saunders' idea seem so different, and why did it garner an enormous amount of attention? Perhaps it was because of his willingness to put pen to paper — to make the unwritten, written. For while social contracts can be implicit (e.g., raising one's hand in class to speak), ones that are explicit (e.g., the U.S. Constitution spelling out unalienable rights of life, liberty, and the pursuit of happiness) tend to carry much more weight. I applaud Saunders' approach toward self-regulation. But more importantly, I applaud his willingness to transparently share the story behind the story with you — our readers (see page 16). For as interesting as it was to see a biopharma CEO take the path less traveled when it came to tackling drug-price increases, it is even more compelling to learn the process and speed in which he and Allergan were able to move their social contract from concept to publication. L

Life Science Leader

SEPTEMBER 2017 VOL. 9 NO. 9

LIFE SCIENCE LEADER
5340 Fryling Rd., Suite 300
Erie, PA 16510-4672
Telephone: 814 897 7700
Fax: 814 899 5587

WWW.LIFESCIENCELEADER.COM

CEO
Jon Howland / Ext. 203
jon.howland@lifescienceconnect.com

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

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

EXECUTIVE EDITOR
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

EDITORS
Louis Garguilo
louis.garguilo@lifescienceconnect.com

Bob Marshall
bob.marshall@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Anna Rose Welch
anna.welch@lifescienceconnect.com

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

STRATEGIC PARTNERSHIPS/BUSINESS DEV.
Mike Barbalaci / Ext. 218
mike.barbalaci@lifescienceconnect.com

Tim Bretz / 724-940-7555 / Ext. 123
tim.bretz@lifescienceconnect.com

Cory Coleman / 724-940-7555 / Ext. 125
cory.coleman@lifescienceconnect.com

Scott Moren / Ext. 118
scott.moren@lifescienceconnect.com

Denise Mosley / 724-940-7555 / Ext. 126
denise.mosley@lifescienceconnect.com

Shannon Primavere / Ext. 279
shannon.primavere@lifescienceconnect.com

Perry Rearick / Ext. 263
perry.rearick@lifescienceconnect.com

Ray Sherman / Ext. 335
ray.sherman@lifescienceconnect.com

Tracy Tasker / Ext. 297
tracy.tasker@lifescienceconnect.com

Derek Van Slyke / Ext. 217
derek.vanslyke@lifescienceconnect.com

Casey Weed / Ext. 219
casey.weed@lifescienceconnect.com

DATA ANALYTICS
Rick Miller
rick.miller@lifescienceconnect.com

Kevin Morey
kevin.morey@lifescienceconnect.com

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

Finesse

part of Thermo Fisher Scientific

Next stop: Never.

Continuous processing speeds up production and brings down costs.

Today, more and more biopharma companies are moving to continuous processes for their small- and large-scale operations. Find out why manufacturers are turning to Finesse products for their continuous processing solutions. Finesse solutions include a universal control platform, plug-and-play flexibility, and the expert integration you need to get going fast. We'll also customize systems to fit your existing infrastructure, so you can keep expenses low. Learn more at www.finesse.com.

LSL

ASK THE BOARD

Have a response to our experts' answers? Send us an email to rob.wright@lifescienceconnect.com.

PERIODICALLY THROUGHOUT THE YEAR we check in with our editorial board and ask them some questions we think our readers will find interesting – and more importantly – useful.

One of our board members, Francois Nader, gave us some great answers to three of our most common questions, so we thought we'd do something a little different this month and run all three questions and his answers. And remember, if you have any questions for our board, send an email to rob.wright@lifescienceconnect.com.

Q What were some of the most valuable lessons learned during Shire's acquisition of NPS Pharmaceuticals?

A
- the incredible payback of practicing the Scout motto, "be prepared"
- the value of having established a seamless and trustworthy board/management relationship
- the importance of a cohesive and efficient management team that continued to run the business while a small group was focused on managing the attack
- communicate, be present, be transparent

Q Knowing what you know now, what if anything, would you do differently in approaching your career?

A Don't be tempted by tactical opportunities and golden handcuffs at the expense of your dream. While it might serve others, it does not necessarily serve you progressing toward your personal goalposts.

Q What are some of the most interesting insights gained from serving on a corporate board that have made you a better leader?

A
- the strategic importance of the board and management synchronicity
- the criticality of governance and board culture
- taking the time to develop and assess the "what if?" scenarios and challenge the status quo
- the humility of accepting that you are not in the driver's seat: management is!

FRANCOIS NADER, M.D., MBA
is chairman of the board at Acceleron Pharma. He is the former CEO of NPS Pharmace and serves on several other corporate and philanthropy boards.

Q Could a value-based drug pricing system lead to higher drug prices?

A **IN THIS TYPE OF SYSTEM,** drug companies are paid only when the prescribed drug works for a patient. The fear is that drug companies will have to raise their prices to subsidize the lost revenue that comes from all the instances where a drug did not work for a patient. Biopharma companies are going to be forced to offer guarantees about their drugs in order to justify inclusion of their new – and expensive – drugs in formularies. While list prices might increase as a result of such programs, the fact is that negotiations between drug companies and payers are pretty intense and generally lead to prices that both parties can live with. Thus, I don't expect that attempts to raise prices because of the need to reimburse for those patients for whom the drug failed will be a viable strategy.

JOHN LAMATTINA, PH.D.
is senior partner at PureTech Ventures. Formerly, he was senior VP at Pfizer and president of Pfizer Global Research and Development.

OneSource Laboratory Services: With you every step of the way – to reach *your* best outcomes

In today's complex scientific environments, every lab function has to work in sync toward a common goal. Our OneSource® Laboratory Services team delivers solutions that cover all aspects of your operations and can be customized for the scientific workflows and business outcomes you're striving toward. With proven success at the world's top pharmaceutical and environmentally focused organizations, and managing more than 500,000 assets worldwide, the OneSource team provides a complete services offering with global reach and local support. Together, we're taking business results to the next level.

Learn more at www.perkinelmer.com/onesource

PerkinElmer®
For the Better

Part D Is Due For A Tune-Up

JOHN MCMANUS The McManus Group

Dear reader, I had the Irish Luck of serving as staff director of the Ways and Means Health Subcommittee for then-Chairman Bill Thomas (R-CA), and I was tasked with developing, negotiating, and drafting the Medicare Modernization Act of 2003 (MMA), which added the Medicare Part D drug benefit.

It was a brutal process for members and staff alike. We passed different iterations of the bill three times in the House in as many years before the Senate finally took it up. Chairman Thomas then led an intense, five-month conference committee (often working 12-to-14 hour days) where we hammered out differences between the House and Senate bills and even added some new ideas, for example, means-testing in Medicare. (I remain convinced that abandonment of this deliberative process, requiring negotiation and consensus building, is a major reason for the current dysfunction in Washington.)

The bill passed with a center-right coalition, losing our right flank of archconservatives but picking up several dozen Democrats in both chambers despite firm Democratic leadership opposition. We reached out to the healthcare community, soliciting their input and ideas and integrated policies to strengthen rural hospitals, create tax-free health savings accounts, and crack down on fraud and abuse.

Of course the heart of the bill was the market-based Part D drug program, which looked nothing like traditional Medicare's top-down approach and raft of regulations and fee schedules. At the time, the notion of a stand-alone prescription drug plan was totally alien, and we had substantial concern whether enough plans would show up to provide sufficient choice and competition. That problem never materialized in Part D – there are currently 746 plans across 34 regions. But a paucity of plans has plagued the exchanges established by the most consequential healthcare law since the MMA — the Affordable Care Act.

Most impressive has been Part D's performance related to cost control. A few weeks ago Health and Human Services Secretary Tom Price announced that the average monthly premium will decline by over a dollar next year to $33.50 in 2018.

The remarkable thing about that figure is that during consideration of the MMA, Republicans defeated a Democratic amendment, which would have *required a $35 monthly premium for 2006 — 12 years ago*. That amendment attempted to lock in the CBO (Congressional Budget Office) projection for the average premium for all plans in 2006 because they preferred a government guarantee rather than the prospect that a competitive market could deliver a product at a cheaper price. Thank goodness, it was defeated: Seniors will be paying less in 2018 for their drug premiums than Democrats would have forced them to pay in 2006, more than a decade later.

Lost in the hubbub over drug pricing has been the flat and declining spending recently in Part D. The CBO's June 2017 Baseline Projections show that Part D spending stabilized at $95 billion annually for 2016 and 2017 and will decline to $92 billion in 2018. Costs have stabilized, in part, because $117 billion of products are going off patent and the volume of Hepatitis C prescriptions has declined as patients are cured and go off therapy.

PROBLEMS BREWING

The CBO projects renewed cost escalation in 2019 and thereafter and predicts costs will double within 10 years. The CBO has been wrong before — overestimating Part D costs by 45 percent in its initial estimate — yet

industry experts know that the pipeline is brimming with promising specialty medicines that will cost a lot of money and a growing population of seniors who will demand access to these cures and innovative therapies.

Moreover, the Part D premium should not be the sole metric of success of the program. Patient access to therapy and their out-of-pocket cost sharing must also be examined.

Specialty tiers and cost sharing increasing

One key problem is the administrative creation of "specialty tiers," which prohibit the appeal for coverage of drugs that cost more than $670 and require substantial cost sharing of between 25 and 33 percent. This policy has no basis in the statute but has been left unchanged since its creation in 2005. The result is that physicians and the beneficiary cannot appeal for lower cost sharing even if that product is the only medicine that works for the patient.

The use of specialty tiers has become more ubiquitous, and cost-sharing obligations in Part D have become more onerous recently. While specialty tiers have been utilized by a number of plans throughout the 12-year history of the program, *all* prescription drug plans started utilizing a specialty tier for the first time in 2015 and every year since then, resulting in substantial cost sharing for beneficiaries that utilize such drugs.

According to an Avalere analysis, 58 percent of covered drugs face coinsurance, up from 35 percent just a few years ago. Although coinsurance has historically been applied to only specialty-tier drugs, more PDPs (prescription drug plans) are applying coinsurance to drugs on lower tiers, including the nonpreferred brand tiers. The percent of beneficiaries enrolled in Part D plans with more than one tier requiring coinsurance has skyrocketed to 96 percent in 2016 from 39 percent in 2014. Coinsurance on expensive specialty drugs is much more onerous for patients than flat copays.

Growing DIR not benefitting patients

On the final day of the Obama administration, CMS issued a report on direct and indirect remuneration (DIR) — manufacturer rebates and pharmacy fees collected retrospectively from PBMs (pharmacy benefit managers) and Part D plans after the patient has been dispensed the drug. It found that DIR nearly tripled between 2010 and 2015. But CMS appears to have substantially underestimated how much is provided retrospectively. Its report estimated $17.4 billion in DIR savings in 2014 but the PMBs' own analysis by the Oliver Wyman consulting firm estimated $31.7 billion in "negotiated savings." Where is the missing $14.3 billion? Either CMS does not know or the PBMs are overstating their savings.

In any case, patients are paying inflated copays on the list price of drugs that do not reflect the substantial price concessions manufacturers provide through rebates. This has the effect of pushing patients through the benefit faster, resulting in expedited access to the catastrophic benefit where Medicare pays 80 percent of the costs and the plans pay just 15 percent. This means any rebate that exceeds 15 percent is straight revenue to the plan once the catastrophic is hit, a real policy concern flagged by the Kaiser Family Foundation: "Medicare's reinsurance payments (for spending in the catastrophic) to plans have represented a growing share of total Part D spending, increasing from 16 percent in 2007 to an estimated 42 percent in 2017."

The statute requires beneficiaries to have access to "negotiated prices" at the point of sale. However, current CMS regulatory interpretation permits price concessions that cannot *reasonably* be determined at point of sale to be made retrospectively. The question is how much can be reasonably determined at point of sale; CMS could take a more expansive view of that, for example, by requiring the preponderance of rebates to be provided at point of sale with an allowance for a squaring up of any discrepancy between estimated and actual rebates at the end of the year.

WHAT CAN BE DONE TO STRENGTHEN THE PART D BENEFIT?

1. Permit manufacturers to provide copay assistance directly to patients rather than through cumbersome charitable foundations. This would require the creation of a safe harbor from the antikickback statute.

2. Reform specialty tiers to allow the appeal of high-cost drugs and eliminate the arbitrary cost-sharing obligations that require a high percentage coinsurance rather than flat copay.

3. Require the preponderance of DIR fees to be provided at the point of sale so beneficiaries can benefit from the price concessions provided for the drug they are prescribed at the pharmacy counter. Actuarial analysis shows this will have a modest impact on beneficiary premiums. 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.

Successfully Transforming An Organization: An Active Approach

RICH DALY

Transitions in pharma and biotech can take on many variations. However, experience offers guidance as to the key factors for success.

In my career, I've had the opportunity to work in just about every type of environment imaginable, starting with a growth company in my first life sciences job. That was followed by a startup; a large, mature pharma; a second startup; and three reorganizations (two large pharma and one biotech). Whether it's moving from clinical to commercial stage, from one product to four, expanding the commercial footprint beyond the U.S., or leading a complete turnaround of a business, each required a transformational approach to ensure success at subsequent stages.

During the first transformational opportunity, I took on a senior leadership role in a turnaround situation — a $3 billion, 2,500-employee company — that had failed to achieve its sales and profit targets in each of the last four years. Within one year, we improved the bottom line and stabilized the workforce by reducing the employee turnover rate from 25 percent to an industry standard 8 percent.

The second transformational opportunity was with a large, U.S.-based business looking for an experienced professional to step in as president of a $1.5 billion, 3,000-person business with the largest, but poorest-performing U.S. portfolio in its therapeutic area. Nine months later, we consummated a major merger simultaneously with the launch of two new products and grew the bottom line without downsizing or layoffs, transforming the portfolio into the fastest growing in the United States.

The cumulative knowledge gained from these and other experiences provides me with insight into some of the key factors that drive success in a transformation as well as how to prioritize the factors in each situation to optimize the potential for success. Based on my experiences, there are four key elements necessary for success in transformational situations:

- Financial strength
- Execution
- Talent
- Strategy

While each is important to the success of the organization, frequently in a transformation we find ourselves short of time and unable to act on all four. Urgency forces us to quickly assess the situation, determine the areas of greatest need, and prioritize based on the unique elements in each situation. The limit of the most vital commodity — time — drives us to the most important one or two needs that matter most to the success of the company.

THE FINANCIAL STRENGTH REQUISITE

A transforming company can be a challenging financial entity. Whether it's transitioning from clinical to commercial, experiencing a turnaround, or expanding its footprint beyond its home borders, there are likely daunting challenges.

Critical to success are talent, strategy, and execution. However, experience has taught me to dissect the financials first before progressing to the other elements. Understanding the financial structure and strength (weakness) of a company is the first step to success in a transformation, as it allows the leader to allocate and align resources for the journey.

Finance is a language unto itself, and to know it is

to truly be bilingual. Beware though; there are traps. There's an old accounting axiom that is insightful for the uninitiated:

- Income statement: all the lies a company tells.
- Balance sheet: where the company hides all the lies.
- Statement of cash flows: where the company is forced to tell the truth.
- Understanding all three as well as the historic budgeting process is essential.

THE STRATEGY IMPERATIVE

Naturally, a well-conceived and -executed strategy is critical to the success of every venture. Unfortunately, transformations oftentimes are not afforded the luxury of time to craft a detailed strategic position. It can often feel like we're "building the plane while we're flying it." To rapidly uncover core strategic advantages, we concentrate our efforts on the concept of *uncertain imitability*, that is, what is it about us that is hard to copy. It's a common-sense approach that recognizes that strategy arises from the combination of activities and can be revealed by three fundamental questions:

1. What do we do that no one else does?
2. What do we do that everyone else does, but we do differently?
3. Is it sustainable?

These questions are simple, but they are not simplistic. By guiding an experienced internal team through this exercise, leaders can produce powerful, long-lasting results.

THE EXECUTION ESSENTIALS

Ideas are easy. Execution is hard. Two things matter most in this area:

First, *we are all patients serving patients*. This foundation should drive a consistency through a shared mission, vision, focus, messaging, and resources. We're lucky that our industry has a built-in people mission — we help people to live better lives. By aligning around shared values, we can keep the silo walls low. Silos destroy our effectiveness and ability to execute. Break them down whenever and wherever you can through overt communication.

Second, make sure people know their job matters and, above all, make sure they are expected to act like it. The patient is waiting. What have we done today to deliver high-quality solutions to patients (and their families) in need?

THE TALENT ASSET

Greatness is found at the intersection of the common good. It's about the people — internally and externally — your organization serves. If a transformation is a turnaround, the employees can easily be forgotten and left behind. There's a school of thought that promotes cleaning house and starting from scratch on the people front. I am not enrolled in that school. The clear majority of people want to engage in a positive and productive manner. They want to contribute to a successful endeavor.

My experience has been that in a struggling organization, there are people inside who know things — people who see things. In fact, it's often the middle managers, the people who own the "real estate" in the company, who can make things happen — or block you.

For a successful transformation, a leader needs converts. The balance comes in the form of patience. That is, even in large organizations, by picking the right people, winning over just one or two a day you can dramatically shift an organization. During a transformation, there may be a segment of employees aligned with you (say 20 percent), there are those who may disagree (20 percent), and those who are not sure (60 percent). Your role as a leader is to win over those on the fence. After all, those aligned with you are your champions. Those who disagree will be best swayed by momentum — not by you.

ALL GOOD IDEAS SEEM LATE

Urgency is everything in a transformation. There is pressure from above, below, and even outside the organization. Successful transformations are achievable with the proper mix of all four elements mentioned previously. Each transformation is unique and requires a thoughtful diagnostic to reveal the right mix of the elements for success. Time is never on your side, so you must triage carefully and pick the most urgent need and build from there. Eventually you must incorporate all four elements, but it is unlikely that you can be successful if you spread your efforts too thin. L

RICH DALY, chairman and CEO of Neuralstem, has leadership experience across nearly every biopharmaceutical function and over the last 25 years has had commercial success in 10 therapeutic categories.

Arena Pharmaceuticals

Rebuilding to develop a large shelf full of in-house discoveries

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Arena Pharmaceuticals has reemerged as a developer of new "best-in-class" drugs: e.g., ralinepag (APD811) completed a Phase 2 trial for treating PAH (pulmonary arterial hypertension); etrasimod (APD334), in Phase 2 for multiple autoimmune indications including ulcerative colitis; APD371, in Phase 2 for pain associated with Crohn's disease. Another drug, nelotanserin, in Phase 2 for Lewy Body Dementia, is partnered with Axovant Sciences.

WHAT'S AT STAKE

If at first you *do* succeed, you still might have to try again. Success in this business usually means arrival at a milestone — proof-of-concept, clinical development, Phase 3 completion, and perhaps market authorization if a company thinks that far ahead. But few companies reach the point where their products face the toughest test, on the market with an approved indication. Arena started up 20 years ago as a pioneer of GPCR (G protein-coupled receptor) technology. It eventually discovered and developed Belviq (lorcaserin), for weight loss in treating obesity and subsequently marketed the product through its partner Eisai. Unfortunately, and perhaps indicating the unattractive nature of the indication, Belviq and competing products launched about the same time tanked in sales. Arena had succeeded in raising money based on projected Belviq sales of more than $1 billion worldwide, but when the actual turnover turned out to be less than $100 million, the company was left with little revenue despite a burgeoning pipeline of new compounds coming out of its discovery group. Belviq commercialization also had distracting structural effects on the company.

"Essentially the company ended up looking a little bit like a barbell," says president and CEO Amit Munshi. "On one side, Arena had this fantastic discovery research on GPCRs, and on the other side, the company was largely focused on Belviq and commercializing the drug for obesity."

By early last year, Arena's board decided to remake the company, beginning with new management and a new strategy. It soon brought in Munshi, who quickly sized up the situation. "My fundamental premise was actually quite simple: While the whole world was focused on Belviq, the discovery resource platform on GPCRs continued to progress with novel, potentially best-in-class compounds into early clinical development. I looked at the products that were essentially sitting on a shelf, and I said to the chairman and board of directors, 'If I come on board, we have to rebuild Arena as a development company.' Since then, we've brought the company back to a core drug development platform."

The surgery was somewhat radical. Arena divested all Belviq rights to Eisai, replaced 90 percent of its management and 70 percent of all personnel, and closed down its discovery group entirely to concentrate on building up the development function. "We had more than enough to work on as a company — a rich basket of compounds," Munshi says. "Substantial" investor interest in the company rebuild has driven two strong financing rounds so far in 2017, he says.

Arena has no plans to reinstate a discovery research group in the extraordinary case it somehow brings all of its products to market with all potential indications. But if you're worried about what happened to the company's proud team of leading GPCR scientists, there is a possible happy ending — with the ongoing Beacon Discovery incubator. "When we terminated discovery research, we allowed the individuals to spin out Beacon as a small, independent resource group, which does some work for us on a contract basis. We also have a right to look at compounds they produce to see if anything is of particular interest for us." Another lesson from Arena: Even when you succeed with a new strategy, never stray too far from your old friends.

AMIT MUNSHI
CEO

Vital Statistics

100
Employees

Headquarters
San Diego, CA

Finances

Public company
$75M
from stock offering in April 2017

$162M
from stock offering in July 2017

Research partnership funding
Collaborations with Eisai Co., Ltd. and Eisai Inc., Axovant Sciences, and Boehringer Ingelheim International GmbH

Latest Updates

July 2017:
Received positive Phase 2 results for ralinepag, an oral, selective, next-generation IP receptor agonist targeting the prostacyclin pathway, in treatment of pulmonary arterial hypertension (PAH).

Evolve with flexibility

Deployment of single-use technologies throughout your facility enables you to achieve optimal performance and efficiency. Our innovative single-use bioprocess technologies enable you to implement systems, from cell culture to downstream purification, while providing the ability to quickly scale operations.

Apply GE single-use solutions to expand your capabilities and accelerate your bioprocess journey.

gelifesciences.com/singleuse

GE Healthcare Bio-Sciences AB, Björkgatan 30, 751 84 Uppsala, Sweden.

29215291 AC 04/2017

BRENT SAUNDERS
Chairman, President, and CEO, Allergan

BEHIND THE SCENES OF ALLERGAN'S SOCIAL CONTRACT

ROB WRIGHT Chief Editor @RFWrightLSL

Allergan CEO fires back on Hillary Clinton tweet."

That's how CNBC titled an interview between Brent Saunders, Allergan's chairman, president, and CEO, and Mad Money host Jim Cramer back on September 21, 2015. The tweet in question, referencing Turing Pharmaceuticals' significant price increase of a 62-year-old drug, read:

Asked by Cramer for a response to the tweet, Saunders replied, "The example she tweeted about today was just one egregious situation. I think we have to separate the one-off kind of situations with what really happens. And, keep in mind, we need to have good pricing to create innovation."

Suddenly Saunders found himself squarely in the crosshairs of presidential politics and its laser-like focus on blasting biopharma for its "high-priced" drugs.

Just under one year later, Saunders was once again observing a developing drug-pricing scandal as senators Chuck Grassley (R) Iowa and Amy Klobuchar (D) Minnesota focused the drug-pricing spotlight on Mylan for its price increases of the EpiPen. "Mylan and Turing were anomalies, and it really bothered me that an industry so committed to helping people live better lives was being viewed so negatively by the public," attests Saunders. It was August 2016, and Saunders was on the "first true vacation" he had taken in roughly 17 years. "On the flight I started thinking about industry's commitment to finding equilibrium between the need to invest in innovation and pricing treatments so they are accessible and affordable," he recalls. And while Saunders had previously used the term "social contract" to refer to this notion of balance, it was while on vacation that he was able to crystalize his thinking. What follows is the story behind Allergan's bold decision to formalize its social contract with patients.

Vacation Sparks The Idea Of A Social Contract

Much like many executives, Saunders says he finds it difficult to turn off the business portion of his brain during the downtime of a vacation. Thus, the genesis of the social contract creeped into his mind during that first flight of his family vacation. After ruminating on the idea for the next few days, he eventually decided to call some of his colleagues back at Allergan to get their opinions.

What, If Anything, Would Brent Saunders Do Differently?

When pressed as to what, if anything, he would do differently in developing the social contract, Saunders has few regrets. "Had we done a press release or made it an editorial, we would have likely had to cut back on the wording, but a blog allowed us to put it out there in black and white so people could see it in its entirety," he says. "But if I could change or add something, it would be to create more balance regarding how the social contract deals with pricing." He says many people focused too much on the commitment to not increase drug prices more than 10 percent. "It is not about getting to a 9.9 percent increase," he explains. "If you read beyond the headline you will see that our intent was to increase only the price of our medicines in line with medical inflation, and the double-digit number was a cap, not a target." As such, Saunders says if he could do anything differently, it would have been to add more emphasis to the section that dealt with investing in R&D to meet an unmet medical need or highlight the expansion of Allergan's patient-assistance programs, which, by the way, have had a 30 percent increase in the number of inquiries following announced enhancements in December 2016.

The first three on his list were Alex Kelly, EVP Corporate Affairs and chief communications officer; Bill Meury, EVP and chief commercial officer; and Bob Bailey, EVP and chief legal officer and corporate secretary. He picked these three because he thought they could provide the most help in terms of developing the first draft of the social contract.

"First, I did bounce the idea off my wife, in terms of how she thought it might be received," Saunders admits. Articulating it with her and the other family members on the vacation further convinced him he was on to something. "It was a pretty big group, my in-laws, my parents, my brother and sister and their families. The social contract was not the theme of this vacation, but there was a lunch where various family members shared their positive and negative views of the biopharmaceutical industry and what could be done to improve it." As many of his extended family work in healthcare as providers, they hear the voice of the patient and know how difficult it can be to prescribe a medicine that insurance doesn't cover or requires a lot of paperwork and prior authorizations.

The initial reactions of both his family and work colleagues further solidified his general notion that the industry needed to do more to show all the good it does. Now he just needed to refine the concept and put it into action.

Refining And Gaining Support

When the initial small team first started working on the social contract, the goal was not to make any kind of public statement. "We started working on it not really knowing where we would ultimately take it," Saunders admits. The original thought was to see if there was something that could perhaps be constructed as an industry code or maybe even define some kind of standard just for Allergan.

"There was a lot of back and forth as we tried to write down principles we felt were not only important to Allergan but could help define where we stood on fairly sensitive and controversial issues in the public press," he shares. For example, one of the areas where there was a lot of pushback and debate was around the social contract's take on raising the price of medicines near the end of a patent-exclusivity period. "Many in our industry tend to take more price increases at the end of a drug's life as a means of managing the difficult financial impact caused by loss of exclusivity," Saunders explains. While such price increases can have an impact on patients, there was some discussion as to whether these types of increases were really a burden primarily borne by insurance companies. "We debated that for several days and ultimately agreed the right thing to do, and the place where we felt most comfortable, was operating in an absolute commitment around pricing versus taking a piecemeal approach," he explains.

Saunders returned from vacation toward the end of August, at which point the team had a pretty good draft of the social contract. "It was then that I started to share it more broadly with the rest of the Allergan executive team to get more feedback," he explains. Saunders did not want to have a group meeting yet, as he wanted everyone to feel comfortable talking through what it meant. "I did not want anyone to feel there was group pressure, as I was hoping to get very casual and candid feedback," he continues. "So I started calling each executive leadership team member individually." Due to vacations, work schedules, and work travel, it took him a few days to meet one-on-one with all the executives. Overall, their responses were positive regarding the social contract in general and how it was written, but there was some debate over when it should be published. "They reacted so positively that I thought maybe we should just share it with the whole organization," he says. But before it could be shared with 18,000 employees, making the social contract essentially a public document, Saunders needed to first share it with Allergan's board of directors. "I sent it out to our board and then began calling to get their feedback, which again, was overwhelmingly positive. As the executive management and board of directors embraced the social contract, Saunders felt the company had something that accurately depicted the way Allergan (collectively) felt about the drug-pricing issue. "Our next step was to share it with our employees and the public, but we had to be willing to stand behind it," he explains.

An Informal Exercise, Not A Structured Plan

There are plenty of businesses with corporate value statements; J&J's Credo is one industry-specific example. But Allergan didn't use any of those other documents as a model for creating its social contract. In fact, Saunders says that when they started developing the social contract, "We were not viewing this concept as being core, and we did not have a predetermined output. We were simply trying to think about how to memorialize the social contract, what it meant to Allergan, and how we could hold ourselves to it."

He says that, because it began as an informal exercise, no "real research" (that he is aware of) was done to model it after something else.

"I get asked about the social contract all the time," Saunders chuckles. "Executives and CEOs from other biopharmaceutical companies seem to think Allergan had a committee — a project plan — and that we engaged in some very deliberate strategy to put this thing out." That couldn't be further from the truth, though. Instead, he says it was more of a spontaneous process put in motion by a very small group that then spread it to the highest levels of the organization. When Saunders shares this with other CEOs and explains that from start to finish the entire process took less than a month, they are astounded. "Some have stated that if they tried to do what we did at Allergan, it would have taken months, if not years."

Now, one year after the publication of the social contract via a Sept. 6, 2016, post to his CEO Blog, Saunders has the benefit of hindsight. "If we had turned the development of the social contract into a massive project with lots of consensus building, I think we would have diluted the commitment, overanalyzed the wording, and perhaps extended the period in which it would take to get it out." He says the social contract really expresses his views, as well as those of the senior leadership and board at Allergan, and as such, has become much bigger than he ever imagined. "I was doing a town hall meeting for one of our new subsidiaries, LifeCell [a regenerative medicine company acquired by Allergan], and the social contract was probably one of the primary things discussed amongst those colleagues," he shares.

Indeed, the continued interest and positive commentary surrounding the social contract still surprises Saunders. "The day we published it via the blog, I quickly got a sense that it was going to get a lot of attention," he relates. "But I never thought it would have such a meaningful impact to our colleagues globally." When they first began the social-contract

Where Did You Come Up With The Term "Social Contract"?

Throughout 2015, Brent Saunders, chairman, president, and CEO of Allergan, was a very busy executive. For example, in March 2015 the Actavis-Allergan acquisition was completed. In July 2015, he inked a deal to sell the company's generic business to Teva Pharmaceuticals for $40.5 billion, the largest deal in Israeli corporate history. In October of that same year, Allergan began merger talks with one of the biggest biopharmaceutical companies in the world, Pfizer — potentially a $160 billion deal. As such, Saunders found himself in high demand for financial-oriented talk shows.

On Nov. 4, 2015, Saunders appeared live via a satellite feed on CNBC's Mad Money, hosted by Jim Cramer. As the Pfizer and Allergan talks were in the preliminary stages, Saunders wasn't able to discuss any details. But the day previous, top House Democrats announced the launch of the newly formed Affordable Drug Pricing Task Force aimed at taking meaningful action to combat skyrocketing costs of pharmaceuticals. "Jim Cramer asked me on the air what I thought about it," Saunders recalls. This is live banter, so the questions were not provided to Saunders in advance. "In my off-the-cuff response, I used the term 'social contract,' and that stuck with me," he explains. Here's exactly what he said:

> *"If we are going to talk philosophically about this, I believe pharmaceutical companies have a social contract in America, to make sure we continue to invest money in R&D, to raise drug prices in a very responsible way, and make sure we can grow our business for our shareholders. And I believe all those things can live in harmony, and in the vast majority of the pharmaceutical industry they actually do."*

Saunders has since given some thought as to why the social contract concept came out of his mouth that day. "I think it goes back to some of my time at Schering-Plough and working with Fred Hassan," he shares. "When Fred shared his view of the world as a pharmaceutical company leader, he always talked about the importance of being socially responsible in how an organization does things. Over my life sciences career, I have had similar learnings from other people as well, and so that concept has probably been in my heart and mind for a long time."

exercise, it was viewed as more of a U.S.-centric initiative, yet as time went on, the concept resonated loudly with the company's global field sales force, as well as their customer physicians. "We never thought that audience would be so interested in it," he confides.

In addition to publishing the blog, Allergan sent letters to its B2B customers, pharmacy benefit managers (PBMs), health insurers, and pharmacies and even took out a few ads in various newspapers announcing the social contract. "That was the full extent of how we planned to promote the blog, outside the use of social media," he attests. A month or so after it was published, Saunders was at the American Academy of Ophthalmology (AAO) annual meeting in Chicago. For a few hours he worked in the exhibit booth and conducted one-on-one meetings with ophthalmologists. "I had hundreds of customer interactions, during the course of which I began asking if they were aware of our social contract," he explains. "Almost every person said yes, pointing to the commitment of not increasing drug prices beyond 10 percent." But when he asked if they had read the whole contract, as there were other important elements (e.g., expanding Allergan's patient assistance programs, the company's commitment to education), most answered no, explaining they were only aware of what they read in the press.

At the same time, the sales reps who were working the booth asked Saunders if he had any pamphlets on the social contract they could share with their doctors. Since he did not, and since he was scheduled to be at the meeting for another day or two, he decided to call the company's head of communications to see how quickly they could put together a pamphlet for sales representatives and customers who wanted to read the whole social contract.

As there was no specific drug mentioned in the social contract, the pamphlet did not have to go through the traditional sales-aid approval process. "We didn't proactively plan the development of a sales aid, because the social contract wasn't developed for that purpose," he explains.

The Risk Of Doing The Right Thing

At the time of the social contract's publication, the United States was nearing the conclusion of a bitterly contested presidential campaign. As such, there was some risk to Saunders putting himself — and his company — squarely in the drug-pricing spotlight. "To be fair, we did have at least one or two conversations around that, but we didn't spend a lot of time worrying about it," he admits. "Within the social contract, we acknowledge that in the past we did not follow these exact rules, but we would be doing so going forward."

As for the risk of putting himself out there, Saunders says, "To be honest, I really don't care. I know that may sound a bit cavalier, but I feel very strongly about our industry's need for a social contract, and as CEO, it is part of my job to articulate what that means for our employees and customers."

Besides, Saunders didn't view this as being all that risky. "I view risk as deciding what R&D projects to fund," he continues. "If we are going to spend several hundred million dollars on something that may or may not work, that is risk. Deciding what acquisitions to go after, what combination of ideas to pursue, which leaders to promote from manager to vice president, or vice president to executive vice president, those are all risks. But I do not view doing what is right and standing up for what you believe in as taking a risk."

Every quarter Allergan conducts town hall meetings for all employees where quarterly performance and other developments are discussed. Coincidentally, the day after the blog was published was the day of a town hall meeting. "That was the first time I saw how the employees really connected with the idea of the social contract and the pride they had from their company taking a position on some really important issues. That definitely ranks as one of the most gratifying experiences I've had in my biopharmaceutical career," he says.

Some Highlights Of Brent Saunders' Career

- **Facilitated Schering-Plough's acquisition** of Organon BioSciences for $14.4 billion
- **Served as integration head** for the $41.1 billion merger of Schering-Plough with Merck
- **Executed the sale of Bausch & Lomb** to Valeant Pharmaceuticals for $8.7 billion
- **Facilitated Actavis' acquisition** of Forest Laboratories for $28 billion
- **Turned hostile takeover attempt of Allergan by Valeant Pharmaceuticals** into a $70.5 billion acquisition for Actavis, and retained the combined company under the Allergan name.

VISIT US AT BOOTH 311
September 24-27 at SCDM

Looking for an experienced and collaborative research partner? **Chiltern is Designed Around You®.**

At Chiltern you are key, because you are at the center of what we do. As you strive every day to bring better, more personalized products to market for your patients, we strive to provide you a better, more personalized experience than any other CRO.

We're building clinical development solutions around you — your program, your investigators, your patients.

CHILTERN
Designed Around You®

Connect with Chiltern

U.S. +1 910 338 4760
Europe +44 0 1753 512 000
Chiltern.com

Chiltern. A Collaborative Approach Designed Around You®.

Clinical Development • Medical & Scientific Affairs • Data & Analysis
Pharmacovigilance • Strategic Regulatory

P3s

How To Get The Good... WITHOUT THE BAD

ROB WRIGHT Chief Editor @RFWrightLSL

At this year's BIO International Convention in San Diego (June 19 – 22), I moderated a session, *Navigating A Clear Path To Public-Private Partnerships*, and we talked about the good, the bad, and the ugly of P3s. After a brief introduction, the first question was posed, resulting in the following edited dialogue.

PANELISTS

STACEY ADAM, PH.D., scientific program manager for cancer, Foundation for the National Institutes of Health (FNIH)

CHANDRA RAMANATHAN, PH.D., VP and head of East Coast innovation center, Bayer

ISSI ROZEN, chief business officer, The Broad Institute of MIT and Harvard

CLOSE TO ZERO.

That's the probability of one company or researcher successfully finding cures for the likes of ALS, Alzheimer's, or any of the other horrible diseases that continue to ravage humanity. To develop therapeutics of the future will most likely require the launch of a number of P3s (public-private partnerships) — today. But just getting a cadre of participants even interested in participating in a P3 can be a challenge, not to mention the process of launching and managing a P3 all the way through to conclusion. For example, the $230 million Accelerating Medicines Partnership (AMP) that was launched in 2014 involves two government organizations, 10 biopharmaceutical companies, and a dozen nonprofits. And while P3s are intended to be part of the solution, if not properly managed they could become part of the problem. How does one prevent such a scenario?

Which P3s Are You Involved With?

STACEY ADAM, FNIH: One P3 that's just coming out of a design phase is the Partnership for Accelerating Cancer Therapies (PACT). It's one of the 41 projects proposed by the Cancer Moonshot initiative, and its purpose is to establish a P3 to help coordinate the ongoing immuno-oncology (IO) efforts with those of the National Cancer Institute (NCI). There are approximately 1,300 IO trials taking place, but some people fear there are not enough cancer patients to actually complete all of these trials, which tells us that we need to improve how we rationally design and coordinate these efforts. Fellow panelist Chandra Ramanathan, along with 41 of his scientific colleagues from 14 separate companies, the NCI, FDA, and a number of academic leaders collaborated on a six-month design phase. The process included 35 separate teleconference meetings and two face-to-face meetings with all participants assembled. We hope PACT to have about $210 million in funding, split equally between the public and private sectors.

An example of a more thoroughly developed project is the Lung Master Protocol (Lung-MAP), a clinical trial for patients with advanced squamous cell carcinoma. Lung-MAP is a P3 involving government (NCI), physicians (SWOG, a cooperative group within the National Clinical Trials Network), patient advocacy (Friends of Cancer Research), seven pharmaceutical companies, and Foundation Medicine (FMI). Thus far we have successfully tested five separate drugs and enrolled over 1,300 patients into the trial, with 500+ of those being allocated to separate substudies. We are expanding that trial to include IO combinations for PD-L1 refractory patients by adding three trial arms in the next year and bringing in six additional corporate partners.

CHANDRA RAMANATHAN, BAYER: We developed an open innovation platform along with a Grants4Targets initiative, which has two arms — pharmaceuticals and crop science. The global research grant program for pharmaceuticals supports research on novel drug targets for application in Bayer's focus areas (oncology, cardiovascular, and gynecological therapies) through funding, expertise, and technologies in drug discovery. Thus far, our open innovation platform has been in place for the last seven years, generated 3,575 ideas from 60 countries, and has funded 285 (and counting) projects.

One of the successful P3s we developed at Bayer was with the American Association for Cancer Research (AACR). The collaboration (AACR-Bayer Innovation and Discovery Grants) promotes the key tenets of the Bayer Grants4Targets initiative, providing new treatment options for cancer patients with high unmet medical need, encourages innovation and translation of ideas from basic research into novel drugs, and fosters collaboration between academia and biopharma. This innovative partnership brings out the best of two worlds — couples the scientific excellence of AACR with drug discovery expertise of Bayer to enable translation of scientific ideas to address patient unmet needs. In addition to funding, there is a mentorship component to educate scientists in principles of drug discovery and development.

ISSI ROZEN, THE BROAD INSTITUTE: The Broad Institute engages in P3s, like the one we have with Bayer, to allow us to propel treatment forward. In seeking to participate in P3s, we look for partners that first, share a specific scientific vision. Second, we look for P3 participants who are willing to share in the commitment, not just the excitement. Sometimes partners of P3s, while enthusiastic, may be a little naïve about the level of resources, timelines, and effort that will be required. The third component we look for is a cultural fit (i.e., organizations we think we can work with effectively). Biopharmas are typically driven by goals, timelines, or bonuses at the end of the year tied to moving "X" number of programs. Academic institutions generally don't think this way and do research until they solve the problem and then publish a paper. Successfully executing a P3 involving biopharma and academia involves finding likeminded people who understand these differences and are willing to work together to bridge them. The Broad Institute will never take a drug into the clinic or into the market because we simply aren't built to do so. But we do have significant capacity to understand biology and targets, and we have a lot of interesting early-stage drug discovery capabilities. So partnering with a company that actually knows how to take a drug to the clinic, design clinical trials, and market a drug is very important to us, as it helps us toward fulfilling our mission.

How Do Government Organizations Measure P3 Success?

ADAM: I think of the FNIH as being the neutral third party that helps broker deals and get the companies and government organizations what they need out of P3s (e.g., drugs progressing into the clinic, moving forward with the FDA, creating guidance documents), while still being able to retain all the IP and licensing rights for our academics to publish. If you are going to establish a partnership with the FNIH and the NIH, all of the data has to be made public. There can't be exclusive licensure to any one person/entity, because the NIH wants the broadest possible use in the clinic or anywhere else. Another metric for us is adherence to all the federal regulations and guidelines.

What Can A City Or Economic Region Do To Promote The Development Of A Regional Cluster?

ROZEN: We have a cluster in Kendall Square near Boston. From my perspective, the success of this cluster began with first having super academic institutions. On one side of the square there is MIT, while on the other side you have Harvard. Just across the river there is Harvard Medical School, Mass General Hospital, the Dana-Farber Cancer Institute, and five other teaching hospitals. So there is an incredible amount of fundamental research happening within a very short distance, leading to a lot of advancement in understanding of basic science. As the world started to believe in biotechnology, we saw the formation of different biotech companies in the area (e.g., Biogen, Genzyme, Vertex). These early successes attracted VCs seeking to invest in opportunities arising from the area universities. Big Pharma saw what was happening in Boston and wanted to figure out how it might benefit. The first Big Pharma to move into Kendall Square was orchestrated by Mark Fishman. Back in 2002, Fishman, the head of the Novartis Research Institute, decided to move the company's research headquarters from Basil, Switzerland, to Kendall Square, and other Big Pharmas soon followed. And while this created a bit of a snowball effect, I don't think the success we have seen in Boston would have happened without the surrounding academic institutions serving as a pipeline for ideas.

RAMANATHAN: While there are public and private institutions that can drive investment, what is also needed is a catalyst (e.g., Massachusetts Biotechnology Industry Organization [MassBIO], Massachusetts Life Sciences Center) to make sure the stakeholders interact and work with each other.

ADAM: There are other cities that have done this that don't necessarily have the big-name institutions. For example, Kansas City has been trying to recruit people to build a bio hub around the University of Kansas Medical Center, and it has been the Kansas Department of Commerce that has been the catalyst.

ROZEN: Phil Sharp is a Nobel laureate professor at MIT and the founder of Biogen. Back in the 1970s, people in Cambridge, MA, where Biogen was started, were very worried about this industry, as they didn't really understand what biotech did. Sharp helped explain to the city council that what would be happening in the labs of biotechs would be no different from what was already happening in the labs at MIT and Harvard. He has a clip from a city council meeting that shows there were a lot of questions. As he responded to their challenges they became more comfortable with the idea of biotech. That was a critical moment for Cambridge. For had he not been able to convince people that the work of biotech was okay, the cluster may not have ever gotten started. Local politicians and governments play an important role in the success of a hub.

Have You Ever Been Involved In A P3 That Started Going Sideways, And What Did You Do To Get It Back On Track?

RAMANATHAN: To avoid a P3 from getting off track in the first place, you need to establish value and flexibility. Understand the value drivers for each partner in a P3, and allow for flexibility throughout the life of a P3, as these often run for many years. For example, how researchers currently approach drug discovery and therapeutic strategy could be very different from what is being done five years from now, and you want to be flexible to adapt to such changing conditions.

ROZEN: If I think about all of the P3s that did not go so well for us, it was often a result of a leadership change on the biopharma side. This is one thing we have found to be very frustrating. A lot of time has been spent creating excitement, aligning scientific visions, building relationships, and working together, and then about a year in one person leaves. A new person comes in, and they have very different ideas of how the P3 should look. Such situations can be very challenging, and I don't have a good solution other than asking biopharma to be more consistent in their strategy involving a P3.

ADAM: In addition to the company leadership, we find it beneficial to have a company champion. Often, that champion is somebody with boots on the ground. So even if there is turnover at the leadership level of a P3, having a company champion can be helpful toward preventing such a change from slowing the P3 down. As for flexibility, I don't think the goals of the P3 have to be overly flexible. However, there should be flexibility in the parameters used to drive successful execution of the P3 and transparent and frequent communication among P3 partners.

How Do You Manage Extremely Large P3s With A Wide Variety Of Participants?

ADAM: It is essential to define the value each P3 player brings. What is it you need to do together? Why does each partner need to be there? If they don't have a need or a value to be at the table, they have less incentive to stay for the long term. Next, you need to define the parameters for P3 stakeholders (i.e., shared benefit and shared risk). Again, everybody is taking on some amount of risk, and so your hope is that a rising tide will raise all boats, as far as the benefit being gained from participating in the P3. The certain amount of risk in a P3 has to be balanced by the idea one partner could possibly have done it faster or better by going it alone. Make sure the P3 has concrete goals and parameters outlined in the very beginning.

We encourage infinite amounts of transparency in the partnerships we run. The first time you start having isolated conversations with any one of the partners, the P3 can begin to get away from you. The FNIH has very clear parameters and guidelines for people interested in working with the NIH, which have to be agreed to up front. If considering doing a P3, consider taking a similar approach of making sure all goals and guidelines are defined in advance.

In getting a P3 off the ground, we prefer in-person meetings. Having everyone sitting across a table from each other and engaging in clear dialogue can work wonders. If you have to do a P3 via telecom, that's where somebody like me comes in. To make sure everyone gets their say, I ask questions of each partner during the call, and do a lot of email follow-up to make sure each partner got what they needed from the teleconference. In addition, I want to make sure we have the right parameters and that these are agreed upon and locked down before moving forward. The last thing I or the P3 needs is for someone (e.g., a financial investor) to say, once we are well underway, that this is not what they wanted.

If A P3 Achieves Its Defined Objective, Should It Be Disbanded?

ROZEN: My experience is that if the partnership is successful, it doesn't die; it morphs, and it can morph in a number of ways. For example, four years ago we started an oncology collaboration with Bayer. It was going so well that we expanded it to include cardiology and basically copied the exact blueprint of what we had in place for oncology. Here is another situation. Over 10 years ago we started the RNAi consortium, which recently entered its fourth iteration. It started out as a three-year consortium with one set of companies. We expanded the consortium two times by adding additional companies. But between the third and fourth iterations, the world changed, and RNAi was no longer the hottest thing, and we had pretty much exhausted this field of study. But we felt that all of the players were getting a lot of value from the consortium. So, instead of disbanding, we changed our focus toward the new hot thing — CRISPR, and changed the consortium name to the Functional Genomics Consortium. It's now generating new value in a different scientific area.

Who Should Someone Call If Interested In Starting A P3?

ADAM: If you would like to start a partnership with the NIH, consider contacting the FNIH first. The advantage of coming to us is that we know the ins and outs of NIH and can usually get you to the right people pretty quickly. If you're doing a P3 with the NIH and it is not a one-company-and-NIH scenario that a simple cooperative research and development agreement (CRADA) can handle, the FNIH will end up helping you navigate it anyway. If you don't know who to contact at either the FNIH or NIH, a good place to start is with the chief of staff of the institute director. These people have the broadest perspective of what's going on within any of the 27 institutes at the NIH. For example, if you want to do a P3 in cancer, get to the chief of staff of the National Cancer Institute (NCI). There is also a P3 panel within the Office of the Director at the NIH that can assist you.

How Should Someone Approach Developing A P3 Within A Biopharmaceutical Company?

RAMANATHAN: There is no magical formula for determining how to make a P3 successful within a biopharmaceutical company. However, when thinking about the various partnerships in which I have been involved, there are five things that you can do to help set you on a path to success. First, be very clear on the business objective. What exactly do you want to get out of the partnership and the timeline? I think that should be really clear before you even initiate the process. Second, you've got to have a champion in the company. This person needs to be passionate about the cause and really believe in what you're trying to do. Third, set expectations well in advance. When you are working with the FNIH and some 40 other people, you have to set an expectation that is similar to doing precompetitive research, and sometimes things take time. Fourth is communication. Keep communicating within the organization so people do not forget what you are trying to do. It can take six months to a year to get a P3 to move from the genesis of an idea to the point where something is actually being done, and if you don't communicate routinely, when you approach the eighth or ninth month, people can forget what exactly you are trying to do. Lastly, whenever you go to meetings and talk about the P3, anchor it to the value — the business objective for why you're doing it in the first place. P3s provide wonderful opportunities to learn from people outside of your own organization and to work on projects too big for one company to handle.

Is There A Good Example Of An Effective International P3?

RAMANATHAN: There is a P3 called Innovative Medicines Initiative (IMI) in Europe, which is a $5.3 billion P3 lasting over 15 years. It is probably the biggest P3 in the world, with 50 percent of its funding coming from the EU, while the remaining 50 percent comes from different companies. IMI focuses on trying to make the drug discovery and development more efficient and targets its priorities by first looking at the priorities of the WHO. Companies can participate in IMI by giving money, sharing compound libraries, or providing people to work on projects.

Parting Pearls Of Wisdom

At the end of the session, each panelist was invited to share a parting pearl of wisdom.

ROZEN: The Broad Institute has looked at many P3s between academic institutions and for-profit entities, specifically pharma and biotech. To be honest, many of these have failed because they were not managed appropriately within the academic institutions or pharma companies, or the structure was not optimal. Structures where one party does all the work while the other comes in every few months to provide feedback don't work because one party isn't fully invested and doesn't understand the challenges. We believe the structure that allows you to increase the probability of success requires all parties of a P3 to have an ownership stake. Our most successful collaborations are those having scientists on both sides with joint responsibility for success.

RAMANATHAN: Power of partnership. For example, there has been lots of buzz around immuno-oncology. However, the reality is, IO currently benefits about 15 to 20 percent of all cancer patients, while the other 80 percent still don't have an option. One company alone cannot address this huge unmet medical need. There is power in collaboration, and the forming of P3s will not only enable the development of new innovative options, but will do so quicker.

ADAM: A shared vision and a shared goal are probably what you want more than anything else. A P3 benefits from strong management and clear parameters for how to achieve the goal. Finally, you need transparent communication from start to finish among P3 partners. If you can hit those factors all along the way, you should be successful. L

FILLED WITH EXPERTISE

Richard's Unique Expertise Meets Your Demanding Biologics Fill and Finish Needs.

Richard is one of the many manufacturing technicians at Althea that deliver the highest quality drug product to our clients on a daily basis. At Althea, we are aware of the innate properties of biologics and we have a strong understanding of how fill finish processes and equipment can affect quality and stability. Our technical experience, combined with an impeccable regulatory track record, enable Richard and the Althea team to meet your most demanding biologics fill and finish needs.

Learn more. Visit AltheaCMO.com

ALTHEA | THE POWER TO MAKE®

A MEMBER OF THE AJINOMOTO GROUP

11040 Roselle Street, San Diego, CA 92121 | 1.888.425.8432 | 858.882.0123

PROCESS DEVELOPMENT • DRUG SUBSTANCE MANUFACTURING • DRUG PRODUCT MANUFACTURING • ANALYTICS • HPAPI & ADC

ROBERT BLUM
President and CEO,
Cytokinetics

THE
ENTERPRISERS

Life Science Leadership In Action

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

CYTOKINETICS: Keeping Its Sights On Independence

PUBLIC COMPANY (NASDAQ)

MARKET CAP: $639M as of August 4, 2017

CASH: $332.1M on June 30, 2017 (cash, cash equivalents, and investments)

STARTUP YEAR: 1998

NUMBER OF EMPLOYEES: 130

FOCUS: Applying the science of cytoskeletal proteins to developing new agents in muscle activation

Can a biopharma company have a soul? If so, the soul should be one that endures. "The biology is the soul of our company," says Robert Blum, president and CEO of Cytokinetics. "We have pioneered an area of biology — muscle activation — proven to offer a compelling pharmacology. Being the experts in the underlying science has enabled us to develop our expertise in the clinical research, and hopefully also affords us competitive advantages in the potential commercialization of our investigational medicines."

Blum speaks today from the farsighted perspective of a persistent company builder, determined to keep the Cytokinetics enterprise on an independent track. We first met much earlier in his company's 19-year history, when it was just beginning to hunt through its founding science on cytoskeletal proteins for pharmacological targets and possible areas of application. Following the most promising path as it unfolded, the company repeatedly narrowed its search to arrive eventually at its area of focus: the mechanics of muscle biology, a key component adversely affected in numerous conditions, including ALS (amyotrophic lateral sclerosis) and heart failure. Many startups spend that much time failing in their original missions and starting over in new directions. But the Cytokinetics story is not about running to ground and reinventing the company. It is about implementing a long-range business plan long enough to see it through. Cytokinetics wants to maintain its independence right onto the commercial stage, taking its own products to the market and aiming for full integration, even as it now partners extensively with Astellas and Amgen in research and development.

INDEPENDENCE WAY

The first duty of a CEO is not only to understand the company's science, but learn how to explain it. Blum introduces the concept of the cytoskeleton, essentially the structural network inside individual cells, as succinctly and clearly now as he did at our initial meeting.

"Besides giving a cell its shape and organizing its parts, the cytoskeleton is a series of proteins involved in cellular activities that relate to mechanical movements," he says. "How a cell divides, moves across a space, and communicates or coordinates with other cells, as when muscles contract — all are a function of cytoskeletal proteins that work together in networks. It is almost like an urban planning system for a cell, in which the proteins move along highways to carry cargo from place to place."

In a decades-long collaboration, four scientists at Stanford, UCSD, and UCSF had pioneered research into the biochemistry of cytoskeletal kinetics and hatched the idea of turning the science to a medical purpose by founding a company. Instead of just jumping into fundraising and wading into business management, however, the scientist-founders recruited seasoned industry talent.

"On their own, our founders determined in 1997 the need to industrialize this promising area of academic research," says Blum. "They knew their pioneering work had pharmaceutical relevance, but it had never been industrialized, and they thought it should be. So, they sought out employees like me who had successfully built companies, and together we found sources of capital." Starting with business development and finance in 1998, he moved on to corporate development and R&D before assuming the CEO position by 2007.

Blum came to Cytokinetics with a set of experiences that would form the "architecture" he would apply at the company over time. From the 1980s, when he worked in sales, marketing, and business planning at Marion Labs and Syntex, through the 1990s, when he cut his teeth on startup construction at COR Therapeutics with mentor Vaughn Kailian, Blum gained some valuable knowledge about managing corporate assets, as in engaging company colleagues and investors.

"I learned a lot about company culture, how to treat people, and how to work effectively with stakeholders outside the company, and that had a meaningful impact on the way I thought about engagement, one to another. With Vaughn, I also learned a lot about how to build a successful biopharmaceutical company focused on a specific area of biology. But ..."

But? Why the but? COR was manifestly successful, developing a category leader with the heart drug, Integrilin (eptifibatide). "But at the expense of a prolific pipeline," Blum says. "Our lack of other new-drug candidates forced us into a position where the best thing for shareholders was to sell the company."

In starting Cytokinetics, the idea was also to focus on one area of biology, as COR had, *but* without over-concentration on a single product. "From the very beginning, we've engineered into the fabric of the company a strategy of building a diverse pipeline of drug candidates, all moving forward together, in

parallel. We can leverage partners, but we will still retain rights, responsibilities, and economics so, as we guide the company's growth, everything doesn't pivot on a single, binary outcome or clinical trial."

The company's commitment to full integration has opened up funding from a variety of sources outside the typical equity financings. "We've raised more capital through partnerships, up fronts, option exercise fees, sponsored research, and development-milestone payments, only occasionally going to the equity capital markets," Blum says. "We have generated a pipeline of income sources that enable us to establish and maintain a leadership position in our area of biology. Our Series A investment round, which closed in 1998, was led by Roy Vagelos at Merck, Bob Swanson at Genentech, and two venture capital firms with complementary experience in building new biotechs."

BECOMING A LEADER

But narrowing the company's original focus demanded the discipline of an iterative process, as Blum describes it. "That is the difference between a biology-centric company and a chemistry- or technology-centric company," he says. "We remained true to the biology, which enabled us to sharpen our focus over time to the specific slice of cytoskeletal biology related to the contractility of muscle."

It was a strategic process as well. "In other areas, the competitive dynamics were too daunting for us to maintain a leadership position. But in the area of muscle biology, we thought we could be the leader and as the company matured, we would have an opportunity to monetize and multiply our investments. Pharmaceutical companies focused on bone health or metabolic syndromes were interested in muscle, and if we were the leading company in that space, we could do deals to leverage that expertise and generate sustainable cash flows to support our diversified business."

When Cytokinetics first went public in 2004, however, it was because the stock market was excited about three drug candidates it had in oncology, in a partnership with GlaxoSmithKline. Yet it soon became clear the company would be unable to achieve or maintain a leadership position in oncology. It would have taken a much more mature and wealthy company to overcome the steep odds in such a crowded area, according to Blum. "A company like ours could not adequately maintain a durable edge in oncology."

An intangible, but perhaps critical, property emerging from the focus on muscle contraction is the expertise and leadership Cytokinetics has achieved in the space, Blum suggests. "We know all the key opinion leaders, we understand the nuances of the regulatory constructs, we know this area like the back of our hand because we have been persevering and innovating in this space for decades," he says.

MUSCULAR PIPELINE

The 2006 decision to focus on activators of proteins involved in muscle function has apparently proved to be a good one, based on the emerging portfolio of pipeline candidates. In Blum's view, they are all first-in-class muscle activators covering a range of potential indications.

The company's oldest and, Blum argues, most valuable development program is for a drug to treat heart failure: omecamtiv mecarbil. Discovered in-house about 15 years ago, the drug activates myosin, the "mechano-chemical" enzyme that powers contraction of cardiac muscle. None of the existing heart-failure drugs safely raise cardiac performance. Some, called inotropes, only used in about eight to 10 percent of patients, boost cardiac output, but also increase heart rate, arrhythmias, and mortality risk.

"We wanted to find a compound that would activate cardiac myosin and increase the duration, not the velocity, of contraction," Blum explains. "By increasing the duration, allowing adequate time for the heart to relax and refill, the drug would achieve an improvement in the efficiency without increased energy and oxygen consumption. We discovered and optimized omecamtiv mecarbil, and during the past 10-plus years in clinical trials mostly conducted by us, but some more recently conducted by our partner, Amgen, we have studied the drug in thousands of patients."

Because the timing of the cardiac cycle is critical, so is dosing, which must stay within a range of 300 to 400 nanograms per ml, according to Blum. "Credit goes to Amgen for helping us develop a modified release form of the drug and a dose-titration strategy that keeps patients reliably in the therapeutic range." Late in 2016, Cytokinetics and Amgen started one of two large Phase 3 trials planned for the next three to five years, potentially to support an NDA filing.

The partnership with Amgen started in 2006 when Amgen purchased an option on omecamtiv mecarbil, and the companies have extended and expanded it several times since then. Blum emphasizes the advantages of the relationship, from the multitude of clinical trials the two companies have conducted, to the terms of their joint commercialization agreement. Their current deal on omecamtiv mecarbil gives Cytokinetics the opportunity to earn total milestone payments from Amgen of more than $600 million, half of which are pre-commercial, as well as royalties on sales in the high teens to the low 20s.

"The royalty terms could be very advantageous to us if omecamtiv mecarbil becomes a multi-billion dollar drug," Blum says. "We have the right to co-fund Phase 3 to buy up our royalty even higher, which we aim to do because it affords us the right to co-promote the drug

in North America, where our sales force will be focused on the acute hospitals and Amgen would be focused on the chronic care outpatient centers. Amgen would be reimbursing us for most of our sales and marketing costs as well, so our royalty would be mostly profit. It's not a profit-sharing deal, in which we would also share any net losses. Amgen is financing the building of our commercial business. It is a very unusual deal structure."

A similar deal with Astellas is helping power the company's most advanced program, for its first-generation fast-twitch skeletal troponin activator, tirasemtiv. When Amgen exercised its option on omecamtiv mecarbil in 2009, Cytokinetics deployed the considerable capital to tirasemtiv development. In plain words, the compound activates the protein troponin in fast-twitch skeletal muscle, as opposed to cardiac or slow-twitch skeletal muscle. Among a dozen or so clinical trials conducted with tirasemtiv, several are in the area of ALS, or Lou Gehrig's disease. A Phase 3 study in ALS, VITALITY-ALS, is now concluding. "If we confirm what we saw in Phase 2, this could be the first muscle-directed drug approved for treating ALS," says Blum.

Most people probably have only a vague idea of what came after Lou Gehrig's "luckiest man in the world" speech at the end of the Gary Cooper movie. In the disease he experienced, the baseball hero could hardly have been unluckier. "Patients with ALS typically die within three to five years, and they die a horrible death," says Blum. The prognosis in ALS is so severe, most neurologists are reluctant to render a diagnosis, instead relying on neuromuscular specialists, he says.

In the United States and Europe, both with a patient population of about 25,000, ALS is an orphan-drug indication with an active patient community. "ALS patients are the most selfless and courageous people you'll ever know, and they're highly motivated to participate in clinical trials, not necessarily to help themselves, but to help the next generation," says Blum. "We've built up a tremendous amount of goodwill, and we have become a leader in the field. This is where it's good to be a small company in a focused area — you can become a dominant player."

Previous treatments under development for ALS centered on saving neurons from cell death. Tirasemtiv takes a different path and would be the first drug to treat the disease by activating muscle, aiming to increase muscle force and power and time-to-muscle fatigue. Tirasemtiv was the subject of four Phase 2a studies in ALS before undergoing the largest Phase 2 study in ALS ever conducted, BENEFIT-ALS, in 2013 and 2014. "The study showed an effect on respiratory function and muscle strength that had never been shown in ALS before," says Blum. "We saw declines that were much less severe in patients on investigational drug than placebo."

According to Blum, slowing decline significantly in ALS would greatly improve patient lives. Life span and the ability to work, feed, dress, and breathe independently all could be extended indefinitely by amplifying skeletal muscle response. For such a small population, the tirasemtiv trials have been unusually large, with more than 700 patients each in the completed Phase 2 and ongoing Phase 3 study. The latter is due to produce its first data by the end of 2017.

About the same time, Blum observes, the ALS Association is publishing a draft guidance document for the FDA — a call for action in accelerating drug development and looking at new endpoints such as the muscle metrics used in the tirasemtiv trials. "The advocacy community, the clinical research community, the FDA — everyone is very motivated — and our study is going to be the first Phase 3 trial to read out in this environment," he says.

SELF-COMMERCIALIZATION

Cytokinetics is prepared to commercialize tirasemtiv on its own in the United States, Canada, and Europe, according to Blum, and Astellas has the option of developing and selling the drug everywhere else. He notes the community of ALS-treating physicians is a concentrated one and, with limited resources and access to capital, Cytokinetics should be able to build a commercial infrastructure and generate a profitable business.

Full integration — taking new drugs all the way through development, winning approval, and then selling them on the market — has always been the plan at Cytokinetics, Blum confirms. A company worth building is one worth keeping, apparently.

"Full integration is an advantage in attracting and retaining employees, allowing us to build a powerful and authentic company culture. Of course, we can't just graft the commercial organization onto the company and maintain the integrity of our science and values. As we move to commercialization, our scientists will be actively involved in sales training, maybe even in sales and marketing, and rather than throwing something over the wall, they will be handing the baton to the commercial group. I've seen this work very well in companies that are the true leaders in other areas. The scientists want to make certain the sales and marketing people understand the story and can articulate it well, and the sales and marketing people have the thought leaders on hand by email or telephone."

Most startup biopharma CEOs, it seems, cannot envision taking a product onto the market. Blum and his team can't envision *not* doing so. The typical "exit strategy" is to get the company into mid-stage development, then license out assets or sell the entire enterprise to a commercial corporation. Cytokinetics wants to write a different story, and perhaps set a different example, for the industry's enterprisers. L

Whistleblower Best Practices

GAIL DUTTON contributing editor @GailLdutton

At some point in the life of a pharmaceutical company, a whistleblower is likely to come forward with allegations of wrongdoing. The intricacies of marketing alone can create a minefield of potential mistakes.

Your best defense begins now.

WHAT THE DOJ LOOKS FOR

"The Department of Justice [DoJ] is focused on ensuring companies constantly monitor operations to determine whether there are compliance problems," Gejaa Gobena, partner at law firm Hogan Lovells, says. Monitoring is tied to a robust compliance program that includes a multiyear audit program and to a culture that encourages employees to report possible wrongdoing.

"Not everything will be captured during an audit, so if a company doesn't encourage employees to come forward, the DoJ assumes the company turns a blind eye to misconduct," Gobena says. "If, on the other hand, a company encourages reporting and addresses issues effectively, the DoJ takes a more favorable view of the company and its intentions."

The main elements the DoJ considers in whistleblower programs are:

- whether the compliance department is adequately funded to do what's necessary
- how independent the compliance department is from the rest of the business
- how much it is respected by the business side of the organization
- how problems are remediated once they are discovered

It's important that investigators dig deeply enough to understand the pervasiveness of a problem, whether the company takes the problem seriously, and how it was remediated. Options extend beyond the surface problem to address the deeper issues by retraining, reassigning, or firing staff.

BEST PRACTICES: SOX AND BEYOND

The Sarbanes-Oxley Act of 2002 stipulates that companies establish whistleblower hotlines. "In 2017, best practices use email, web links, the postal service, and phones," says Kathleen Marcus, former SEC attorney and shareholder at law firm Stradling in Newport Beach, CA.

"When companies set up web links and hotlines, they often promise they'll investigate each complaint. I'd advise companies not to promise how they'll respond, but instead, encourage employees to use the hotline," Marcus says.

"Companies with a compliance officer should have an open-door policy, too," she adds. Face-to-face conversations provide a sounding board and help the compliance officer gather enough information to launch an investigation. It also provides a degree of accountability, ensuring the whistleblower knows a specific person is responsible for investigating concerns.

Establishing an open-door policy and whistleblower hotline are only the beginnings, though.

To mount a robust investigation, you need a comprehensive plan that specifies such details as whether in-house or outside counsel should conduct the investigation, which law firm to retain, strategies to ensure the investigation discovers the root of the problem (if one exists), whom to alert within the company, and practices (especially good record keeping) that protect the whistleblower from retaliation.

"The level of formality in structure and process signals the relative degree of seriousness with which complaints are viewed within a company," says Kent Sullivan, partner at Jackson Walker law firm in Austin, TX, and a participant in the State of Texas' Medicaid fraud litigation against Johnson & Johnson.

Best-practice whistleblower programs should have written policies and procedures that specify contacts. That includes a compliance officer and board-level compliance committee. "Establish effective lines of communication before complaints arise," Sullivan advises.

"I look for other indicia of a culture that allows for and encourages complaints in general. That's a starting point for me," he continues. For a culture to encourage dissent, employees need to know that confidentially will be maintained and that meaningful anti-retaliation policies are not only in place but followed. Corporate training and education programs also should be in place to enhance compliance.

Providing meaningful feedback to whistleblowers also shows companies are serious about resolving complaints. "If you've conducted a sufficient investigation and determined the whistleblower allegations have no credibility, communication becomes key," Marcus says. "If you can identify the whistleblower, it may be important to speak with them about the investigation. Let them know the investigation is completed, the scope of the investigation, and the reasoning behind the conclusion."

When designing a whistleblower program, also consider the form of the final report. Typically, the report will be presented to a special board committee or possibly the full board. Whether companies have written or oral reports may have consequences later. For example, Gobena says, "If counsel can convey findings orally, that may be advantageous. But, if it's necessary to document investigative findings, a written report may make sense if it's written knowing it may be requested by the government later."

ADAPT YOUR STRATEGY GLOBALLY

Companies operating internationally should develop global whistleblower programs. "With the free flow of people and information across borders, this is one of the great challenges of our time," Sullivan says.

Your U.S. strategy can lay the foundation, but compliance programs in each nation in which you operate must meet the highest standards (which aren't always American) and be adjusted for each country. "Ensuring the hotline is in the language of the region is only a starting point," Marcus says. "Consult with local counsel to ensure that nation's requirements are met. For example, France discourages anonymity while the U.S. allows it."

RELATIVE MERITS OF IN-HOUSE OR OUTSIDE COUNSEL

"Either in-house or outside counsel may be appropriate, but it's safer to have outside counsel," Sullivan continues. "Confidentially issues, for example, may be handled easier by outside counsel who can wall off any inappropriate flow of information." Because outside attorneys don't have reporting relationships within the company and aren't located there, they can go where the investigations lead without concerning themselves with internal politics.

Outside counsel also confers greater legitimacy on investigations through its perceived objectivity. Bringing fresh eyes may reveal current or potential problems that may not be evident to those involved in the day-to-day business.

In contrast, in-house counsel's familiarity with the company and its people helps it identify the important elements of investigations quickly.

A hybrid approach, in which in-house counsel hires outside counsel, blends the best of both options. By not conducting the investigation but remaining involved, in-house counsel can guide the investigation so it is more efficient while calming people within the firm. "This provides a very good check for what outside counsel is doing," Marcus says. "Investigations tend to expand." Close involvement of in-house counsel may keep investigations focused on actual risks and thus minimize fishing expeditions.

Be aware, though, that if in-house counsel plays an executive or administrative role, communications with it may not be privileged, Sullivan says. "Working with in-house counsel for whistleblower cases may lead to ambiguity over attorney-client privilege."

Privilege is complicated, and clients often make inaccurate assumptions. The role of in-house counsel is to represent the company — not individual executives, board members, or employees. Discuss the intricacies of attorney-client privilege with your attorney.

WHISTLEBLOWERS REVEAL THE HIDDEN ZEITGEIST

"There's almost always something to learn from whistleblowers, even when they are wrong," Marcus says. Whistleblowers often reflect widespread perceptions. If employees feel they can't talk with their supervisors or that those supervisors ignore their concerns, they may become whistleblowers either internally or by taking their concerns to regulators.

"This is why a whistleblower program is so important," she says. By making it easier to voice concerns, people are more likely to try to solve problems internally without needlessly involving regulators. L

WHEN CONDUCTING A WHISTLEBLOWER INVESTIGATION, PLAN TO ANSWER THESE QUESTIONS:

1. Should in-house or outside counsel conduct the investigation?
2. Which law firm(s) will be retained?
3. How will you ensure the investigation discovers the root of the problem (if one exists)?
4. Who within the company should be notified?
5. What practices (e.g., good record keeping) will be implemented to protect the whistleblower from retaliation?

What To Know If (Or When) The DoJ Evaluates Your Compliance Program

CYNTHIA SCHNEDAR

The United States Attorneys' Manual is an online document prepared by the U.S. DoJ to be used as a "quick and ready reference" by DoJ prosecutors. Thus, corporations generally do not become too familiar with the majority of the manual.

However, the manual has long contained a provision that should be of interest to all corporations. This particular section, entitled "The Principles of Federal Prosecution of Business Organizations," describes factors prosecutors "should consider in conducting an investigation of a corporate entity, determining whether to bring charges, and negotiating plea or other agreements." The principles described in this part are known as the "Filip Factors" because they were revised and expanded in 2008 under the leadership of then-Deputy Attorney General Mark Filip.

Among the nine Filip Factors for prosecutors to consider when deciding whether to bring charges or negotiate a plea, there are two directed at evaluating a corporation's compliance program. First, prosecutors should take into account the "existence and effectiveness of the corporation's preexisting compliance program." Second, prosecutors should consider "the corporation's remedial actions, including any efforts to implement an effective corporate compliance program or to improve an existing one, to replace responsible management, to discipline or terminate wrongdoers, to pay restitution, and to cooperate with the relevant of government agencies."

While the Filip Factors have been around since 2008, the DoJ issued new guidance this past February titled "Evaluation of Corporate Compliance Programs" (the guidance) to be used in conjunction with a Filip Factors examination of a company's conduct. The guidance was issued by the Fraud Section of the DoJ's Criminal Division, a unit that investigates and prosecutes complex white-collar crimes throughout the country. In this latest guidance, the DoJ notes that while corporate compliance programs must be evaluated in the specific context of a criminal investigation, there are common questions the DoJ may ask in making a determination of the effectiveness of a particular compliance program.

The Fraud Section's 2016 enforcement statistics show it concentrated its enforcement efforts in cases involving foreign bribery, healthcare fraud, and securities and financial fraud. However, the principles espoused in the latest guidance apply across all industries, including the pharmaceutical and medical device industries. Corporations can use this guidance, which addresses the 11 key topics discussed below, as an evaluative tool to ensure they have a strong compliance program already in place should they ever fall under the microscope of the DoJ.

1. ANALYSIS AND REMEDIATION OF UNDERLYING MISCONDUCT

When the DoJ becomes aware that a company has discovered misconduct, the company will be expected to demonstrate that it has conducted a systemic evaluation and found the true root cause. The company must show whether it missed prior opportunities to identify the misconduct and what steps it has taken so it will not miss such opportunities in the future. The company must be prepared to demonstrate that its remediation efforts address both the root cause and the missed opportunity to find the misconduct.

2. SENIOR AND MIDDLE MANAGEMENT

The DoJ will want to see that both senior leaders and middle management are engaged in modeling appropriate behavior, addressing the misconduct, and preventing similar misconduct in the future. The company should be able to demonstrate a commitment across the organization to a strong compliance program. At the senior level, the board of directors can demonstrate the independence of the compliance function and of the external auditors by holding

executive sessions with those groups. The board of directors should be able to demonstrate that it is actively examining information it receives and exercising appropriate oversight.

3. AUTONOMY AND RESOURCES

The DoJ will look to see if the compliance function has the stature, resources, and independence to do its job. The DoJ will compare the compliance function to other key strategic functions to see if compensation levels, rank/title, reporting lines, resources, and access to key decision makers are comparable. The DoJ will expect the compliance and control personnel to have appropriate experience and qualifications. It will look to reporting lines and the frequency of meetings to determine if the compliance and control function was operating with autonomy. The DoJ will test for "empowerment" of the compliance function by examining how the company has responded when that function raised concerns. The DoJ will also expect the compliance function to be adequately funded and will assess whether denials of requests for resources were reasonable. Compliance functions that have been outsourced will be closely examined by the DoJ to determine who made that decision and how, how it is being managed, whether the external compliance team has access to the information it needs, and how the effectiveness of the outsourced compliance is assessed.

4. POLICIES AND PROCEDURES

The DoJ will also examine the policies and procedures a company has in place that should have addressed the misconduct in question. First, the DoJ will assess the design and accessibility of these policies and procedures. That assessment will include a careful look at why the policies were designed, how they were rolled out, whether the appropriate employees were involved, whether they were assessed for effectiveness, and whether they were effectively communicated to relevant employees and third parties.

The second aspect the DoJ will assess is the operational integration of those policies and procedures. The DoJ will want to see clear and appropriate responsibility for integrating the policies and procedures, a practice of assessing controls, a determination if better payment systems could have prevented misconduct, a determination of whether the approval/certification process is being used to identify misconduct, and an assessment of the vendor selection process if a vendor has been involved in misconduct.

5. RISK ASSESSMENT

The DoJ will look at what methodology the company is using to identify, analyze, and address its risks. It will want to see what information or metrics the company has collected and how it has used that information in its compliance program. It will evaluate whether the company's risk assessment process accounted for manifested risks.

6. TRAINING AND COMMUNICATIONS

The DoJ will expect companies to have received risk-based training, that is, training tailored to address the risks in the area where misconduct occurred. The DoJ will drill down and examine the form, content, and effectiveness of the training. When misconduct has occurred, the DoJ will examine senior management's communications to employees concerning the company position on the misconduct that occurred. The DoJ also will want to see that resources for its compliance policies are readily available to all employees, and employees are willing to seek guidance.

7. CONFIDENTIAL REPORTING AND INVESTIGATION

The DoJ will want to see that the company has assessed the effectiveness of its confidential reporting mechanism to ensure it is adequately collecting, assessing, and following up on allegations it receives. The company should ensure any resulting investigations are properly scoped and are performed independently and objectively. The DoJ will also expect that the company is using its confidential reporting system to identify root causes and system vulnerabilities and appropriately reporting that information to senior management.

8. INCENTIVES AND DISCIPLINARY MEASURES

The DoJ will expect to see accountability when misconduct occurs. The company must show it took appropriate disciplinary action for misconduct, including disciplining managers responsible for failures in oversight. The company should have an appropriate human resource process in place to ensure the correct persons are involved in disciplinary decisions and that disciplinary penalties are consistent across the organization. The company also should have an incentive system in place, such as granting awards for ethical behavior and denying awards for misconduct, to encourage ethical behavior.

9. CONTINUOUS IMPROVEMENT, PERIODIC TESTING, AND REVIEW

The DoJ will assess a company's internal audit function to see if it is conducting the types of audits that should have identified the misconduct and an adequate audit reporting remediation function to address any reported misconduct. The DoJ will want to examine the control testing the company has performed to ensure the adequacy of its compliance program. The DoJ also will look to see if the company is proactive and is updating its risk assessments and compliance policies, procedures, and practices on an evolving basis.

10. THIRD-PARTY MANAGEMENT

A company should be able to demonstrate risk-based and integrated processes for managing its third-party vendors. The DoJ will want to see that the company has appropriate controls over the vendor, is actively involved in monitoring the third party to ensure those controls are followed, and is identifying and following up on any red flags concerning third-party conduct.

"The DoJ issued new guidance this past February titled "Evaluation of Corporate Compliance Programs" to be used in conjunction with a Filip Factors examination of a company's conduct."

11. MERGERS AND ACQUISITIONS (M&A)

When the misconduct has occurred at a newly acquired company, the DoJ will look to see if the risk of misconduct should have been identified during the due diligence conducted prior to the acquisition. The DoJ will want to see that the compliance function was integrated into the merger, acquisition, and integration process. The DoJ will also want to see that the company continued to track and remediate misconduct during the due diligence process and implemented compliance policies and procedures at the new entities that were formed through the process.

CONCLUSION

The DoJ has long espoused that an effective corporate compliance program can help persuade a prosecutor to mitigate charges or sanctions it is seeking from a corporation. However, now, through its guidance on "Evaluation of Corporate Compliance Programs," the DoJ has given additional insight into how it will determine if a corporate compliance program was effective. Thus, corporations would be wise to use this guidance as a checklist to evaluate their own compliance programs. Using this list not only will help if a company comes under the scrutiny of a federal prosecutor, it will also help build a compliance program strong enough to avoid coming under the scrutiny of the DoJ in the first place. L

CYNTHIA SCHNEDAR, executive VP of regulatory compliance at Greenleaf Health, provides strategic advice to clients in the life sciences industry. She was formerly director of the Office of Compliance for the FDA's Center for Drug Evaluation and Research and served at the DoJ as acting inspector general.

emergent
biosolutions®

BDS Manufacture | Single-use Platform | Aseptic Fill/Finish | Vials & Syringes | Clinical & Commercial

Protected.

Everyone wants to be protected. With Emergent BioSolutions, you can be sure you are. They have a proven track record as a quality provider of contract manufacturing services, for both bulk drug substances and sterile injectable drug products. They are dedicated to one simple mission: to protect and enhance life.

See how Emergent protects lives.

50
PROTECTING & ENHANCING
50 MILLION LIVES BY 2025

ebsi.com/CMO
800-441-4225 | CMO@ebsi.com

Lessons In Collaborating With Big Pharma

ED MISETA chief editor, Clinical Leader @EdClinical

Any small biopharma knows the importance of collaborating or partnering with larger companies and academic institutions. But where do you start, and who should be involved? And what kind of risk should you take on?

Stephen Isaacs, chairman, president, and CEO of Aduro Biotech, has faced these questions numerous times since launching his company in 2008. After all, Aduro's main focus — finding cures for cancer and other autoimmune and infectious diseases — is in one of the hottest segments of the industry today and one rife with partnerships and collaborations.

"As a small company [approximately 175 employees located across two sites in Berkeley, CA, and the Netherlands], partnerships and collaborations are very important to us," says Isaacs. "Regarding Big Pharma, we have partnerships with Janssen, Novartis, and, most recently, Merck. In addition, we work with a lot of academic institutions; we sign sponsored-research agreements in exchange for rights to IP."

FINDING A PARTNER & SETTING YOUR PRICE

When seeking a partner, Isaacs and his team often start by giving presentations at key industry meetings and conferences, which help get their most-promising molecules and data in front of individuals from larger companies. The ASCO Annual Meeting is one such conference in the oncology space. It was at another conference where Aduro's chief scientific officer, Thomas Dubensky Jr., Ph.D., gave a presentation about the company's STING Pathway Activator platform technology, an area of research that holds great potential for the treatment of cancer. The presentation was standing room only. After the presentation, Dubensky was greeted with interest from multiple major pharmaceutical companies hoping to learn more about Aduro's program. Eventually, that interest morphed into partnership negotiations.

"When you have that kind of demand for your technology, multiple interactions with multiple companies help you determine the right price to ask," states Isaacs. "I wrote to each of the interested companies and told them it would cost at least $100 million to sit down at the table. I noted if they were not in the game at that level, we did not want to waste their time. Every one of them came back to us and wanted to talk further." Ultimately, he inked a $750 million deal with Novartis that included a $250 million up-front payment for what was, at that time, a preclinical asset.

WHEN TO SELL? WHEN TO PARTNER?

Generally speaking, the further you can take the research, the better the deal you will be offered in terms of up-front payments, milestone payments, and royalties. But you also have to be aware of the inherent risks. While more data could render a more lucrative deal, not all product candidates make it, and the further you take the molecule, the greater the odds that you will collect data that does not support the primary endpoint.

Isaacs says one of the most difficult decisions to make is deciding when is the right time to sell or partner. The options are:

1. partner now, when I do not have a lot of data and will get a weaker offer
2. wait until I get more data and can secure a better offer, knowing there are risks that could derail the entire molecule before we even make it to collaboration discussions.

"Most of the molecules we pursue in biotech do not work. That is a fact of life. Sell too early and you might get less than you deserve. But wait too long and there is a chance you will get nothing at all. That is a reality you have to consider."

Having encouraging clinical data (Phase 1 or 2 safety or efficacy data) can lead to even more opportunity and, according to Isaacs, bigger checks, which is critical to supporting further development. Because of the time and cost of drug development, getting a partner prior to a Phase 3 study is a goal for many companies.

"Phase 3 trials tend to be very expensive," says Isaacs. "And with Phase 3 trials, it's not just the cost that companies should consider. Subsequent to a Phase 3 trial, the company might get FDA approval. Therefore, companies also need to consider the cost of marketing, sales, and distribution, as well as whether a partner will be needed to help with that endeavor. Companies like Merck, Novartis, or BMS have that well-established infrastructure in place. For many small companies, building that capability would be a daunting task."

"Sell too early and you might get less than you deserve. But wait too long and there is a chance you will get nothing at all."

STEPHEN ISAACS
Chairman, president, and CEO, Aduro Biotech

WHAT ARE THE RISKS?

In striking a deal with a large company, the biggest risk faced by the smaller company might be agreeing to a deal that gives up too much. Regarding the deal Aduro struck with Janssen in 2014, some might question whether the company gave up a valuable prospect in the areas of lung and prostate cancer. Isaacs has a different take on it.

"There are over 200 different types of cancer," says Isaacs. "Lung and prostate cancer are two major indications, but any success Janssen has in those indications will help our overall lab portfolio and, importantly, patients who need new therapeutic treatment options. Additionally, the cash we receive from this deal, which totals up to $817 million and $365 million, respectively, in up-front and milestone payments, goes toward supporting all of our development efforts. You worry about giving something up too early, but although your slice of the pie is smaller, the deal will hopefully make the pie much bigger."

IT'S RELATIONSHIPS THAT *REALLY* MATTER

No deal comes together without first putting in place the right team. Generally, a clinical team and a business development team collaborate. After an initial meeting or discussion takes place at a conference, the development team will get involved. This team also performs a lot of the contract work. The clinical teams from both companies will meet to discuss patients, protocols, and trial conduct.

Isaacs stresses, though, that it is not the business development department that makes these deals a reality. "There needs to be a scientific champion at the big company pushing for the technology. Without that, most of these deals would not happen."

At Aduro, the development team puts a lot of effort into determining the fit between the two companies. "You always have to worry about relationships," says Isaacs. "You can have the best contract in the world, but if the people don't get along, you will have very real problems. I will always approach things first from a relationship point of view and second from a contractual point of view." With respect to the "cultural" differences between large and small companies, he adds, "I think it is too simplistic to say your cultures need to be the same. I have found the culture in two companies will always be different, especially when you are dealing with a large and a small company. It boils down to mutual respect between the individuals involved at the medical, scientific, and clinical levels. Half the battle is getting the personnel involved to respect everyone's opinions. If you have that, you can work through anything."

If Isaacs rejects a deal, it is likely for financial reasons. That said, a number of nonfinancial-related concerns may cause him to pause and reexamine an offer before signing on. For example, the culture of a potential partner might cause him to question whether there could be issues regarding control or direction over the trial. Additionally, in many companies, certain individuals wield a significant amount of power. If during the course of negotiations he or his team gets an indication that a particular individual across the table could be problematic, this might be cause to walk away. He says many of those battles are ones you simply do not want to fight.

Most deals include escalation clauses that outline the steps to be taken to resolve issues that may arise. While the initial responsibility falls within the purview of a joint steering committee, issues that can't be resolved will be advanced to a designated individual at each company for review. At Aduro, that person is Isaacs. "If necessary, I and my counterpart at the other company will sit down over a glass of wine and resolve the problem," he states. "I have yet to encounter an issue we have not been able to solve. The best advice I have is cooperating and communicating with your partner every step of the way. People tend to be very reasonable when the difficult decisions can be made jointly."

Reaching A Turning Point With An Unusual Cancer Therapeutic

K. JOHN MORROW JR.

Sometimes it pays to go against the grain. In 2013 Life Science Leader *published an article describing the efforts of Dr. Ray Takigiku to establish Bexion Pharmaceuticals, a startup biotechnology firm, located in Covington, KY.*

Bexion was one of a number of infant biotechs housed under the guidance of BioLogic, a biotechnology incubator, which has since been reconfigured as a nonprofit umbrella operation. Bexion's headquarters in Covington was taken over by SIDIS, a private investment management company, which continues to lease out the space to several companies, including Bexion.

Takigiku, president and CEO of the company, ignored the conventional rules of biotech startup development in a number of ways. First, Covington is far from the regular biotech hot spots on the East and West coasts of the U.S. This proved to be an auspicious choice, as the company received $500,000 from the state of Kentucky's SBIR-STTR Matching Funds Program.

Secondly, the company chose to renovate a 19th century warehouse rather than build a sparkling new structure from the ground up. Because of the complexities of historic renovations, this approach may drive up the final price tag of the real estate, but does deliver a one-of-a-kind architectural effort. Finally, Takigiku's top choice for a hot new therapy was not a standard chemotherapeutic drug that poisons cancer cells, but rather a substance that appeared to trigger their programmed destruction, or apoptosis.

AN ALTERNATIVE WEAPON AGAINST CANCER

In a recent interview, Takigiku looked back on the events of the last four years as he pursued his "extraordinary idea" that he believed would drive the company forward. During this period, the dozen or so members that make up the Bexion staff have made substantial progress on the development of a therapeutic agent with the present designation of BXQ-350. This substance is composed of two disparate molecules built into a structure known as a nanovesicle. When joined together, those molecules form a potent anti-tumor complex. Cancer cells, unlike normal cells, display negatively charged phospholipid molecules on their cell surfaces. These phospholipids, such as phosphatidylserine, strongly bind the highly toxic nanovesicles. Takigiku and his colleagues hypothesized that the nanovesicles would eliminate cancer cells and leave their normal, nearby companions unscathed. In earlier studies Bexion scientists showed that BXQ-350 killed tumor cells in culture and eliminated human tumors grafted into a special strain of mouse.

A LETHAL AND UNRESPONSIVE CANDIDATE

With the encouraging results from the preclinical work, Bexion has moved to Phase 1 cancer trials, which are authorized by the FDA to consist of a small number of patients, usually in the range of 10 to 30, although in some cases as many as 100. These trials provide an assessment of doses that can be tolerated by the patient without unacceptable toxicity. The therapy will be targeted at patients suffering from glioblastoma, although a Phase 1 trial may accept participants with unrelated conditions. Glioblastoma multiforme is a highly aggressive cancer with an extremely poor prognosis. "We have 10 patients enrolled in our first Phase 1 trial, and we will enroll six more in the coming month or two," Takigiku says. "At this time I can confirm that the pharmacokinetics are as predicted, and the safety profile is promising."

The company is moving ahead aggressively and planning an expansion phase with 30 additional patients. Assuming that portion of the trial generates positive data, Takigiku is hoping to move to a Phase 2 clinical trial sometime in the next calendar year.

Given the very long lag times involved in drug development, many biotech companies struggling in the midst of a new therapeutic modality look to marketing parts of their technologies to generate bridge income. Takigiku recognizes that as a possible avenue for funding.

"We believe our technology has multiple legs, and

there are unexploited leads for us to pursue," he says. "Because of the rapid progress in this area, we are examining these opportunities on a day-to-day basis. We are especially interested in multiple tumor types, as we believe phosphatidylserine is a ubiquitous target in solid tumors. This property bolsters our confidence in its application as a general delivery agent."

Takigiku raised startup funds initially through a group of private investors, which relieves the pressure of an immediate payback from his technology. "We are fortunate to be adequately funded, and as such, we have the luxury to focus on our long-term goal of moving BXQ-350 through clinical trials and to a final approval."

Expanding on his previous comments, he adds, "We now have a defined set of priorities [e.g., all research is focused on cancer] as we move our research forward. We also have the usual interests, such as predictive biomarkers, or other ways to potentially stratify patients."

COMBINING DIFFERENT THERAPIES

The cancer research community, including Bexion, is trying to adapt to the overwhelming focus on the immune system and its manipulation, especially the proteins known as checkpoint inhibitors. These are quite the rage these days as investigators seek to exploit weak points in the cancer cell's wall of defenses. In recent years it has been discovered that this class of proteins, whose function is to dampen the immune response, can prevent the interaction of the T cells and dendritic cells to destroy tumor cells. This elaborate system of checks and balances ensures that the patient's own immune system won't overreact and destroy normal tissue. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to attack and kill cancer cells. A major area of cancer research today involves the use of proteins that block the checkpoint inhibitors, and with two negatives equaling a positive, the T cells are released and mobilized to destroy cancer cells. Monoclonal antibodies that block the interaction between the programmed cell death (PD)-1 protein and one of its ligands, PD-L1, trigger dramatic antitumor responses.

With everything that's going on in cancer research today, Takigiku thinks of present-day therapy as a symphony of responses, in which a number of dissimilar strategies will be combined. "We are focused right now on getting into Phase 2 and in global registration," he offers. "Today there are lots of miracle stories that do provide hope. We want to follow these and be hopeful — but not stupidly hopeful." L

Little Rhode Island Has Big Ambitions To Be A Regional Life Sciences Hub

MICHAEL GOODMAN contributing writer @mikegoodma

Rhode Island's life sciences ecosystem stands at a crossroads. Determined to make a mark as a regional player, it must assemble the right mix of research assets, sufficient infrastructure, and sources of external investment to enable it to stand out from the crowd and attract talent to the Ocean State. Once that engine is engaged, its advocates say, the pieces should fall into place.

The smallest state in the U.S. is trying what few other regional hubs have attempted — to create an ecosystem sandwiched between the behemoths of Boston and NYC that is based on the principle of in-state research spawning homegrown startups. Other ecosystems — Boulder, Miami, Houston — are relatively isolated in their parts of the country, lacking proximity to Big Pharma or to a sizable academic research sector. Rhode Island (RI) has all that, plus a rich, albeit concentrated research base.

UNIQUE ASSETS AND BENEFITS

Brown University and the University of Rhode Island (URI) anchor the academic research sector in RI. The state can also draw from the programs and talent at RI School of Design (RISD), Bryant College, and Johnson & Wales.

In December 2016, Brown signed a letter of intent to lease 50,000 square feet over 15 years as part of a 195,000-square-foot development project by Wexford Science & Technology in Providence's Jewelry District. Brown's Warren Alpert School of Medicine would join Brown's business, technology, cybersecurity, and other professional programs at the space. The Cambridge Innovation Center (CIC), an RI incubator, would be a co-anchor with Brown at the Wexford innovation complex. CIC, which began in Kendall Square in 1999 and has since expanded outside Massachusetts, assists RI entrepreneurs in launching products and companies.

RI Secretary of Commerce Stefan Pryor says, "This innovation complex will be an engine within our new innovation and design district on the Interstate 95 land."

Brown's med school conducts a broad range of research. Pryor highlighted the BrainGate research collaboration, which includes Brown, Stanford University, the Providence VA Medical Center, Massachusetts General Hospital, and Case Western Reserve. The collaboration focuses on research at the brain-computer interface. "An idea is developed and refined at one site and then 'shipped' to a consortium partner where it's independently validated by a different scientist in different trial participants," says Dr. Leigh Hochberg, a professor of engineering at Brown and a neurologist at Mass General.

As a small state with a limited budget, RI has learned to collaborate in regional, multidisciplinary teams. Pryor envisions the state filling a specialized niche in the regional landscape, focusing on bioscience, health/wellness, health/technology, nutrition, software development, design, and textiles. In this model, RISD, for instance, with its human-centric design capabilities and programs in textiles, could join with the URI, which is conducting research into wearable biosensors in its Department of Electrical, Computer, and Biomedical Engineering. The result of that collaboration might enable patients in clinical trials to be continually monitored whether at home, at the clinical site, or at work.

RI's challenge is to take stock of its research assets and figure out a unique way in which they might fit together that doesn't recapitulate its larger neighbors to the north and south.

The state also boasts benefits such as a life sciences labor force (both youthful and experienced) and affordability. Graduates will stay and work in RI's life science ecosystem if there are wet labs and startups waiting for them. In fact, that could also attract youthful talent from out of state, using the state's beaches and historic sites as added inducement.

"This innovation complex will be an engine within our new innovation and design district on the Interstate 95 land."

STEFAN PRYOR
Rhode Island Secretary of Commerce

Pryor stresses that the cost of construction, labor, and of doing business in RI is lower on a relative basis compared with surrounding states. And real estate, especially commercial, is approximately 50 percent less expensive than East Cambridge or NYC.

STARTUPS, OUT-OF-STATE FIRMS, AND INVESTMENTS

A few homegrown life sciences companies dot the RI landscape.

EpiVax. CEO Annie De Groot, M.D. established the TB/HIV lab at Brown as a center for immune-informatics driven vaccine design. EpiVax spun out from that lab in 1998. She has since moved her academic affiliation to URI where she established the Institute for Immunology and Informatics. The firm has an early-stage pipeline of 10 vaccine candidates, many of them based on proprietary Tregitope technology. It has been funded by SBIR and Biodefense grants, and in its early days, by the Slater Fund (an RI economic development fund that operates like a venture fund).

Prothera Biologics. Prothera develops Inter-Alpha Inhibitor Proteins (IAIP) to treat severe inflammation associated with infection and trauma. Its sources of investment include the RI Commerce Corp., NIH grants, and especially the Slater Fund, which recently invested $250,000 in Prothera, bringing its total investment in the firm to $950,000. Prothera's pipeline is preclinical.

Agcore Technologies. Founded in 2010, Agcore specializes in human nutrition and animal feed. Its products, primarily fish feed, are based on Spirulina, a nutrient-dense blue-green algae. Its products are commercial. Investors include RI Commerce Corp. Agcore's algae is also used in biofuels.

RI is also home to several big and midsize biotech companies. Amgen and Alexion maintain manufacturing plants in RI, as does Rhodes Technologies (a subsidiary of Purdue Pharma). The state sees a place in its ecosystem for large, out-of-state drug manufacturers.

J&J is in the process of opening a health technology center in RI, occupying space for 75 employees at 1 Ship St., across the street from the Wexford complex. The state has eased its entry with about $6 million in incentives including $4.1 million in qualified job tax credits. A J&J spokesman said it was attracted by "world-class universities," government incentives including tax credits and access to job training, and proximity to airports and Amtrak.

GE will open a digital information technology center in Providence, hiring 100 data scientists, engineers, and other IT professionals. GE Chief Technology Officer Chris Drumgoole said, "With its unique location along the northeast corridor, Rhode Island gives us access to many of the assets we need for success." The Providence site complements GE's presence in the Fort Point section of Boston.

Virgin Pulse, a unit of Richard Branson's Virgin Group, will expand its workforce in RI, adding 300 jobs and moving to a location in Providence. Virgin Pulse specializes in technology to promote wellness among workers.

Pryor points to J&J, GE, and Virgin Pulse as exemplifying RI's strengths "at the intersection of IT and health."

THE CHALLENGE

RI is engaged in a delicate balance between nurturing its homegrown strengths and tapping into surrounding regional strengths. Pfizer Groton lies to the south. Medtronic and Smith & Nephew have a sizable presence in the Cabot Business Park in Mansfield, MA, while Depuy is nearby in Raynham, MA — both towns lie near the RI border. RI is working closely with MassBIO to determine how the states can combine their strengths and grow a strong Northeast region.

But challenges loom. RI needs to build out lab space. And funding is an ongoing need. The state can help with incentives for infrastructure projects and with vouchers and tax incentives for RI startups, and big institutions like Brown can spin out technology and help fund big projects like the Wexford innovation complex. But RI recognizes that it needs venture funding. Boston VCs are too focused on East Cambridge to pay much attention to Rhode Island. The state would like to entice the venture arms of Big Pharma to seed-fund promising RI research — but for now, that's aspirational.

RI's plan is to exploit its research strengths at the convergence of bioscience and IT. It wants to launch therapeutic and device startups but also to lure additional Big Pharma manufacturing facilities. And it wants to integrate its research expertise in design, nutrition, engineering, and textiles. In fact, it feels like RI is in an experimental mode, seeing what works.

RI is clearly oriented toward the Boston-Connecticut axis. NYC, another emerging life sciences ecosystem, is more oriented toward the New Jersey and Philadelphia axis, home to Big Pharma. Perhaps the future holds an interconnected ecosystem spanning the Northeast from Pennsylvania to Maine?

The evolution of life sciences in the Northeast surely needs a push from state and private actors; but its eventual footprint will be determined by how the regional hubs develop organically over the next few decades. That's anyone's guess. In some form, RI will be part of that unfolding story. L

Preparing For A Blockchain-Enabled World

CAMILLE MOJICA REY contributing wrtier

Ask life sciences industry leaders and experts about blockchain, and you will hear it called everything from "a game changer" to "a major disrupter." According to the hype, the technology behind cryptocurrencies, like bitcoin, is going to completely transform day-to-day operations for life sciences companies.

Blockchain technology, which allows the creation of shared digital ledgers, has been touted as a way to increase supply chain security, decrease human error and fraudulence in clinical trials, and improve postmarketing surveillance. And these are just some of the big-picture problems people expect blockchain to resolve. As blockchain technology is developed, few doubt that it will change the way data is collected and shared within companies, as well as between companies and third parties — such as CROs, partners, and regulators.

"Blockchain holds great promise for the life sciences industry," says George Serafin, national managing principal of Grant Thornton's Health Care and Life Sciences practices. A 30+ year veteran in the life sciences industry, Serafin was involved in writing a Spring 2017 research report, titled *The Future of Growth and the Life Sciences Industry*. The report called blockchain a "groundbreaking technology" that "can be leveraged for a variety of solutions across the life sciences value chain." Serafin says industry leaders need to be clear about what blockchain is and what it is not. "The leadership of more companies needs to become better-educated with respect to blockchain technology. It's not a silver bullet, and it requires significant investment."

Pharmaceutical industry leaders agree. They know a blockchain-enabled world is on the way. A 2017 survey conducted by the industry nonprofit the Pistoia Alliance found that 83 percent of the 120 senior pharmaceutical and life science executives they asked expected blockchain to be adopted in less than five years. Still, only 22 percent of life sciences companies in the Pistoia survey were already using or experimenting with blockchain. "The Pistoia Alliance recognized early on that interest in blockchain among life sciences companies was growing rapidly," says Nick Lynch, a consultant with the organization. As blockchain becomes more widely adopted for storing and sharing data in other sectors, the alliance is responding with educating their members through webinars and special sessions at their annual meetings. Yet their statistics show that the interest has yet to translate into use of blockchain. That's likely because many questions remain unanswered for the average executive: 1) What exactly is blockchain? 2) How can it be applied, both within a company and industrywide? and 3) How do companies prepare for this blockchain-enabled world?

UNDERSTANDING BLOCKCHAIN

Fundamental knowledge is necessary if pharmaceutical industry leaders are to have a more accurate understanding of what blockchain can realistically do and in what time frame. However, the hype around blockchain has resulted in a phenomenon in which few people are willing to admit they don't actually understand how it works. "Not many people understand blockchain enough to tell you what it can actually do," says Daniel Himmelstein, Ph.D. Himmelstein is an expert in biological and medical informatics and a postdoctoral fellow in the Department of Systems Pharmacology and Translational Therapeutics at the University of Pennsylvania. "A blockchain itself is a data structure that allows its users to maintain a distributed database without having to trust each other," Himmelstein explains. Currently, this structure, which can be thought of as a distributed ledger, is primarily used to enable financial transactions

WWW.CAPSUGEL.COM

ENGINEERING MEDICINES TO LIFE

Capsugel®

CHANGING THE FUNCTIONAL ROLE OF CAPSULES IN DRUG DELIVERY

By combining polymer science, engineering and formulation know-how, we are creating breakthroughs in capsule and encapsulation technologies that are changing the functional role of capsules in medical research, drug formulation and drug delivery. Capsugel provides leading-edge solutions that protect high value compounds, optimize delivery to targeted sites in the body, and ensure the best operational performance in capsule filling. With solutions for rapid product development, solubility enhancement, enteric protection, inhalation, pediatrics and colonic delivery, Capsugel provides the broadest product range and unparalleled service for clinical development and commercial supplies.

between participants, but can also be used to store small amounts of data or host programmable money, called smart contracts. Smart contracts are created so that the currency gains logic. For example, this could involve payments with expiration dates or payments that require approval from multiple entities.

One blockchain application encodes a unique hash, or digital fingerprint, of a document into a transaction, thereby time-stamping the document. This method can be used to prove that a PDF, such as a clinical trial protocol, existed at some time in the past. Instead of being stored on a single server, the ledger is stored at each node of the network. The nodes employ consensus protocols, which are the rules by which the network abides. Any new transactions are verified by the nodes. If the data entered do not follow the rules, the new transaction is not accepted. This means, for example, the hash of a time-stamped document cannot be changed later. "Consensus protocols adopted by the network provide security to make the blockchain immutable," says Himmelstein.

Preservation by amber is Himmelstein's favorite analogy for explaining how transactions become secure once placed on the blockchain. "Imagine that a fly becomes trapped in amber and every 10 minutes new amber forms around it. The amber gets larger and larger as time goes on. If you see a huge chunk of amber, you know it's been there a long time." The same goes for data placed on a blockchain. "It's a well-accepted idea in computer science that bitcoin transactions placed on the blockchain are practically irreversible in just a few hours."

The blockchain becomes resistant to change and deletion because it would take an unprecedented amount of computer power to rewrite a past transaction, explains Darryl Glover, a clinical pharmacist and YourEncore expert in the application of blockchain. "You would have to have huge, government-level computing power to change tens of thousands of copies at the same time," Glover explains. The bitcoin blockchain has not been hacked since it was first introduced in 2009. There have, however, been a few instances of breaches in its security. These involved smart contracts that were attached to the blockchain. "You can't update a smart contract. Any bug you have exists forever," Himmelstein says. Smart contracts are a new area of computer programming. "At this point in time, it's hard to create smart contracts without bugs because it's such a new field." Glover says vulnerability lies in anything external to the blockchain. "Company leaders need to be sure to limit this kind of exposure." These breaches, combined with a perception that blockchain is too new to trust, have created some fear of the technology, Glover says. "Blockchain is not new. It's based on cryptography invented in the 1940s and public/private keys developed in the 1970s." What happened is that the people behind bitcoin combined these established technologies in a new and unique way. "There shouldn't be any more fear about implementing the use of blockchain than there is over using Microsoft Office."

BLOCKCHAIN APPLICATIONS

Blockchain works best when it is viewed as complementary to existing systems that generate data a company would like to time-stamp and share. According to Glover, "Blockchain is meant to facilitate, not replace." He adds that blockchain is best used to:

- Build bridges between existing systems, internally or externally
- Create true data provenance
- Know the type of data and be able to trace origin of data
- Create a network of trusted partnerships

"There shouldn't be any more fear about implementing the use of blockchain than there is over using Microsoft Office."

DARRYL GLOVER
YourEncore expert

Widespread acceptance of blockchain will require pharmaceutical makers to transition from the current process-oriented data structure where information about a pharmaceutical product is stored in the databases of every entity that comes in contact with it, from those who supplied ingredients to the pharmacy where the drug is dispensed. Instead, a product-oriented data structure will allow all information associated with a product to be shared on a blockchain. (See Figure 1.) This transition will address a whole host of issues that plague the industry, says James Canterbury, EY global life sciences risk & compliance leader. However, blockchain will not be the answer to every problem, Himmelstein says. "What blockchain networks are good at is providing a new level of trust. You don't have to trust a third party to verify the authenticity of something on the blockchain. This differs from the traditional model, especially in the pharmaceutical industry where almost every

Grifols Partnership

Better together

When time to market is crucial

DRUG MASTER FILE FOR WATER FOR INJECTION

AS A DILUENT, IN GLASS VIALS

Grifols currently produces millions of vials of high quality WFI each year. Therefore, **when your time to market is crucial we already have the solution.**

Since the diluent you choose is just as important as the API, we use a highly automated and specialized production process with the latest technology for manufacturing parenteral solutions.

Grifols has over 70 years of experience in manufacturing parenteral solutions and diluents.

Grifols Partnership is a CDMO focused on sterile solutions and lipid emulsions, which offers experience, manufacturing capability, and guidance to other companies in the pharmaceutical sector.

Available in different sizes from 5 ml to 50 ml.

Contract Pharma September 14th - 15th, New Brunswick
CPhI October 24th - 26th, Frankfurt, Booth **41J52**

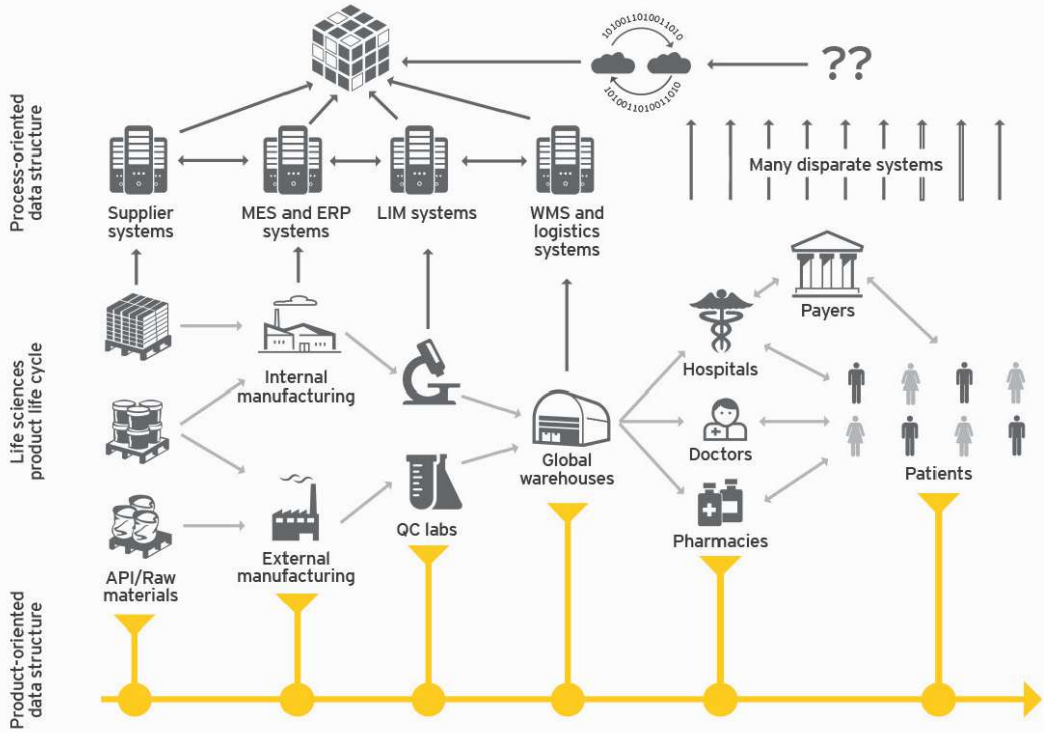
Contact us at: **partnership@grifols.com**
Tel: **+34 935 712 199**
Visit us at: **www.partnership.grifols.com**

GRIFOLS

Grifols International, S.A.
Parc empresarial Can Sant Joan
Av. de la Generalitat, 152-158
08174 Sant Cugat del Vallès, Barcelona - SPAIN
Tel. +34 935 712 199
www.grifols.com

HG/CM/0717/0012

FIGURE 1: PROCESS VS. PRODUCT ORIENTATION OF DATA STRUCTURES



SOURCE: EY

step has some level of trust in it." Pharmaceutical companies have to trust they have purchased pure ingredients or that the CRO they have hired has not changed a protocol, for example. "Some of that trust can be removed by switching to blockchain," Himmelstein says. Only things that are automatable can be switched to blockchain, such as verifying the authenticity of a digital document or tracing the provenance of a token representing pharmaceutical ingredients. "Those things that require human intervention will see less benefit." Below are some of the areas thought to be the most likely to be revolutionized by blockchain networks.

Supply Chain Security. Experts agree that supply chain security is one of the best fits for blockchain technology. In fact, Canterbury says that if bitcoin had been around for 10 years instead of five, companies working to comply with the global serialization requirements that go into effect in November 2017 would likely be doing so with a global blockchain network. "Blockchain missed the boat in terms of timing, but may be a good Plan B for serialization." Canterbury says bitcoin itself is still an experiment of sorts. "In life sciences, before anything becomes official, it has to be proven out extensively — which is a good thing — and that takes time." Canterbury describes what a blockchain would look like for a pharma product in a white paper published in June 2017. Such a blockchain would start with batch creation and follow the product through to the smallest saleable unit. Because blockchains can refer to other blockchains, companies will likely begin with blockchains that collect data from processes that are within their control before including external manufacturers and distributors. According to Glover, counterfeiting in the U.S. happens primarily at the pharmacy level. "What blockchain creates is a single source of truth. You prevent someone from outside the system from inserting false numbers." But, because most attacks come from an internal source, Glover says that biometrics should be married with private keys. "If you verify a person's identity using retinal, finger, or facial scans at the time of making a transaction, there is no way anyone can say that someone took their key."

Clinical Trials. Himmelstein says one issue that would be easily resolved by distributed ledgers would be the problem of the "professional patients," people who volunteer for clinical trials — sometimes simultaneously — without disclosing participation to those running the trials. "The problem with clinical trials as they are now is that when patients enroll, you can't track them from trial from trial." Himmelstein

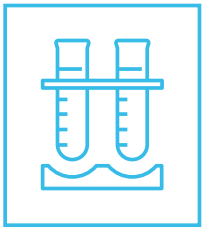
MEET US AT CPhI WORLDWIDE
Stand 80G22 | 24–26 October

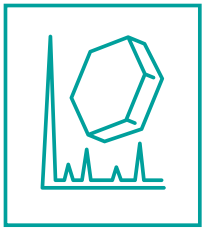
amri
Complex Science. Expert Solutions.

WE'VE GOT IT DOWN TO AN EXACT SCIENCE

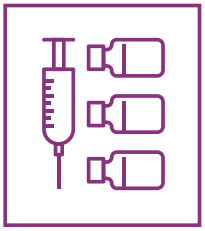
At every stage, AMRI delivers the expertise you need.


Discovery


Development


Analytical and Solid State Services


API Manufacturing


Drug Product

Explore our expert solutions at amriglobal.com

North America • Europe • Asia | 1.518.512.2000

says that at least one drug failed to receive approval because a percentage of the patients in the clinical trial were shown to be in multiple trials. A clinical trial's blockchain would also store investigator data, allowing easy access to up-to-date credentials. Blockchain could also facilitate the transfer of information from clinical sites to CROs and manufacturers. Right now, moving data between systems is a time-limiting step. Most importantly, because of the immutable time-stamping, a blockchain network would improve overall data provenance for clinical trials.

Pharmacovigilance. Blockchain will give pharmaceutical companies the opportunity to proactively gather data. Right now, data gathering on adverse events is reactive. Glover points to the case of one Silicon Valley company that has developed a system that includes ingestible sensors, a small wearable sensor patch, an application on a mobile device, and a provider portal. This is the kind of data, as well as traditional survey data, that would be useful to store on a blockchain. "Now you can start looking at outcomes. If you survey actively, you can detect problems early and avoid an expensive, extensive recall. You can also go back to insurance companies and show that your drug has not required hospital admissions and patients' risk factors are down, etc.," Glover says. Patients would be rewarded for providing data because getting patient-level data and protecting identity is the ultimate goal. If a drug recall were to occur, that data could be matched to serial numbers and only those serial numbers linked to adverse events. "Blockchain could facilitate public safety, while saving drug companies millions in discarded product."

PREPARING FOR BLOCKCHAIN

Pharmaceutical companies large and small are looking at how to prepare for blockchain. It is how they prepare that will make a difference, says Canterbury. "When people in the life sciences start looking into blockchain, they start looking at the industry's big problems," Canterbury says. However, big problems are going to involve large networks that require widespread participation across the industry. Instead, companies need to start by focusing on smaller, internal problems and the networks that already exist within a company. Every company, for example, collects quality metrics around batching. Switching the storage of that data from a database to a blockchain — or embarking on other internal pilot blockchain projects — has its advantages, Canterbury says. "First, companies will have more accurate and reliable ways of collecting internal data. Second, companies will develop teams with the skillsets and the understanding required to be on the forefront of industrywide blockchain applications without having to disrupt everything."

The Pistoia Alliance is advising its members to begin looking for opportunities to collaborate. "Stakeholders — including life sciences companies, tech firms, and regulatory bodies — must begin a dialogue on the creation of industrywide data-sharing standards during this early adoption phase. These standards will improve security and render patients more likely to share their data with companies, benefitting everyone from researchers to patients, both now and in the future," Lynch says. Because the organization's mission includes encouraging collaboration, it already has a legal framework for sharing their members' blockchain experiences in a safe, noncompetitive arena.

For the industry as a whole, significant barriers still remain to the widespread implementation of blockchain, Serafin says. One of those barriers is that companies have significant investments in their current platforms. Once leadership gets on board, there is still the challenge of migrating existing platforms to cloud-based solutions. "The IT departments are wrestling with this now," Serafin says. The most important unknown is how the FDA and other global regulators will respond to blockchain's potential. "Due to its highly regulated environment, the pharmaceutical industry is one that follows, instead of leads. It looks to regulators for the nod of approval. There has been no nod, yet."

Sam Hume, Ph.D., expects that nod to come. "Blockchain may well be next," says Hume, head of Data Exchange Technologies at the Clinical Data Interchange Standards Consortium (CDISC), a nonprofit that develops data standards to foster smarter research and enable connections to healthcare. "Blockchain promises to solve some thorny problems in the industry, especially for regulators. It's too early to say we're working on it, but as our members start to do more development work around blockchain, and as the technology matures, we will work with them to figure out how to make our standards work with their technology." Companies that perform regulated clinical trials are required by the FDA and PMDA (Japan) to submit data using CDISC standards. Increasingly, nonregulated researchers are adopting these standards, as well. This is important because the need for standardization will only increase in a blockchain-enabled world. Hume predicts the widespread adoption of blockchain will be much like what took place when the internet was first introduced. "It took about a decade for web to scale up. It just takes longer when things require cooperation." The transition to blockchain-based systems will be painful at first. "We won't really see the full benefit of the technology until the large blockchain networks are in place." L

OutsourcedPharma
CONFERENCE AND EXHIBITION

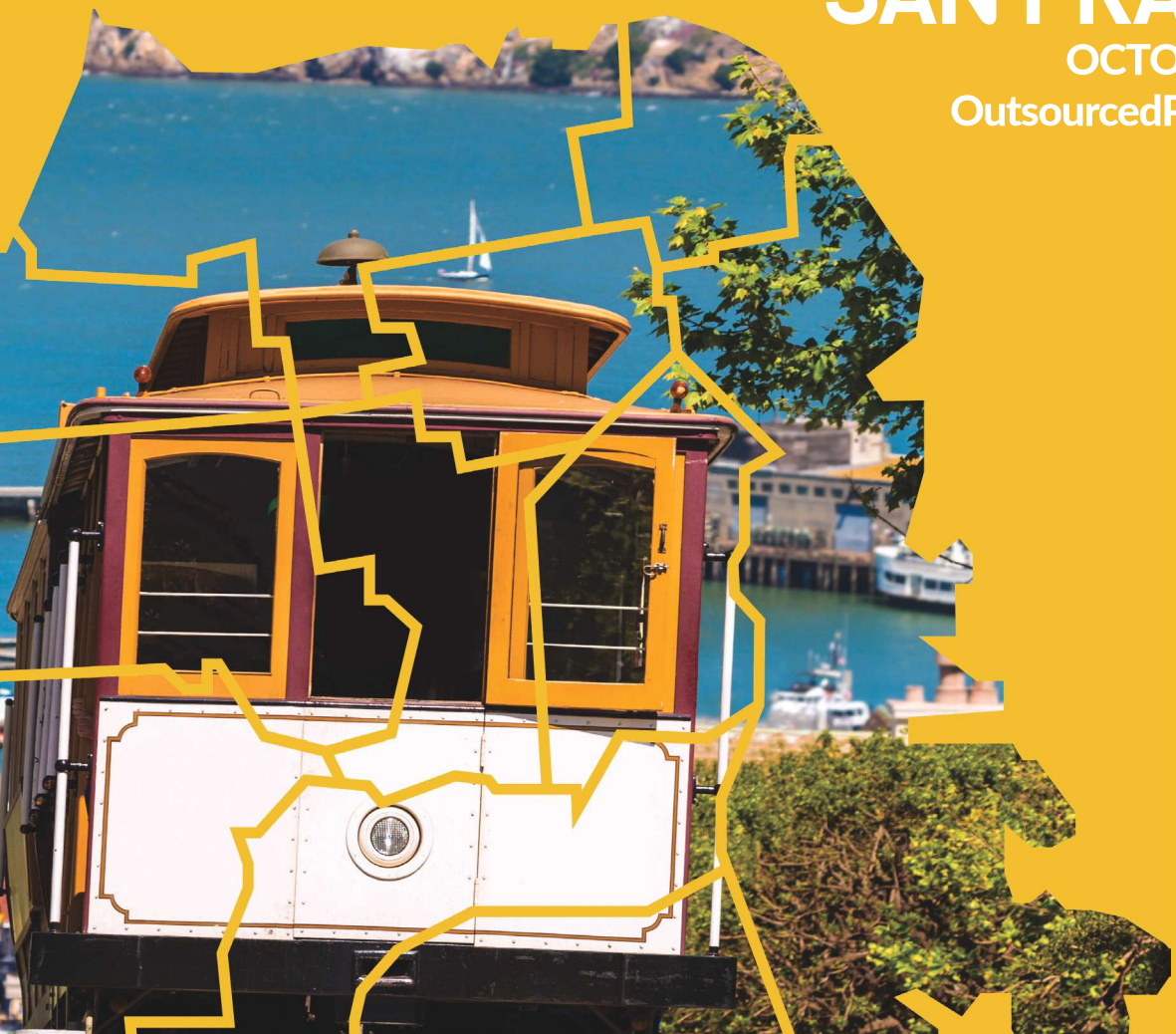
TRANSFERENCE IN DRUG DEVELOPMENT AND MANUFACTURING OUTSOURCING

Produced by *Life Science Leader* magazine and OutsourcedPharma.com, Outsourced Pharma Conference & Exhibition is a vibrant forum for thought-leadership and the application of best practices for professionals engaged in outsourcing drug development and manufacturing.

SAN FRANCISCO

OCTOBER 17 - 18, 2017

OutsourcedPharmaEvents.com



Research Reveals Critical Need To Eliminate Clinical Silos

JIM REILLY

New research confirms that many of the challenges sponsors face managing clinical trials stem from the disparate nature of processes and systems. The *Veeva 2017 Unified Clinical Operations Survey*, one of the industry's largest surveys of clinical operations professionals, indicated that nearly all respondents cited the need to better integrate their clinical applications, including EDC (electronic data capture), CTMS (clinical trial management systems), and eTMFs (electronic trial master files). Faster study execution and improved study quality were the top drivers in bringing together end-to-end processes and systems.

The survey showed that it is common for companies to use as many as four or five applications to manage their clinical studies, with EDC and CTMS being the most commonly used applications. The top two challenges cited — integrating multiple applications and reporting across applications — are a direct result of system silos.

STUDY START-UP CHALLENGES

Both the Veeva study and a separate report from Tufts Center for the Study of Drug Development found that approximately 95 percent of sponsors report challenges with study start-up — usually due to the use of multiple systems and tools. For example, the vast majority still rely on spreadsheets to manage the study start-up process, with roughly one-third or less using CTMS, eTMF, or home-grown applications. Companies that use two or more tools to manage study start-up practices report encountering at least three challenges.

Both studies also found that the time from the pre-study visit to contract execution accounts for the majority of the lengthy study start-up cycle time. Almost two-thirds of sponsors in Veeva's survey say contracting and budgeting are their most challenging study start-up processes. Site identification selection and study planning during protocol design were the next most oft-cited challenges.

MODERN SYSTEMS ARE IMPROVING CLINICAL PROCESSES

New applications and platforms are helping life sciences companies streamline the clinical ecosystem. Trial master file (TMF) management solutions, for example, have experienced rapid transformation during the past four years, with one in three sponsor companies now using advanced eTMF applications, more than doubling since 2014. And 77 percent of sponsors using modern eTMF applications report improvements in inspection readiness and managing the growing volume and complexity of clinical trials.

Similarly, there is also a shift underway with CTMS. A Markets and Markets report forecasts life sciences organizations will increase their CTMS investments by almost 15 percent each year through 2020 as sponsors report significant deficiencies in their current systems. This is being driven, in part, by rising demand for data and site-collection solutions and the greater availability of next-generation CTMS applications.

THE RIPPLE EFFECT

Clinical trials are a critical part of the broader product life cycle, including regulatory, quality and manufacturing, commercial, and medical. As the next big step forward, information will flow through to other parts of the organization and have a positive impact across many areas.

Clinical and other functional groups need to access much of the same data during different stages of drug development. Rather than using redundant, manual processes or complex integrations, cloud-based platforms enable different teams to access the same information in multiple ways.

As the research shows, there is a tremendous opportunity for companies to transform their operations by streamlining their clinical environments. Doing so will undoubtedly drive new levels of efficiency and effectiveness across the entire clinical ecosystem.

JIM REILLY is VP of clinical market strategy at Veeva Systems. For the last 15 years he has held a variety of senior positions in life sciences technology, where he has led software delivery and sales efforts in regulatory, clinical data standards, and content management.

Disrupt Yourself

Before Somebody Or Something Else Does

MARK SANBORN

MARK SANBORN is the president of Sanborn & Associates, Inc., an idea lab for leadership development. Globalgurus.org lists Mark as one of the top 30 leadership experts in the world. He inspires leaders at every level to turn the ordinary into extraordinary.

John, an exemplary employee, was promoted into a key management position. He wanted to address the team he would now be leading and gathered the group together in a training room. The new leader's boss was part of the assembled group.

Thanks to an investment in some formal training and a willingness to prepare, the new manager was an effective communicator. He gave what he considered to be a powerful and successful presentation. The group dismissed and headed back to their respective jobs. The manager's boss lingered behind. He was a stickler for excellence and had a reputation of being tough but fair.

"So what did you think?" John asked expectantly. The more experienced and wiser leader simply said, "I expected more."

If you were John, what would you have done? John recalls, "I stayed in the room and got to work on improving the presentation I just gave."

John had been unsettled by his boss's response, but he didn't simply let it bother him. He chose to disrupt himself and get better.

In my new book, *The Potential Principle: A Proven System for Closing the Gap Between How Good You Are and How Good You Can Be*, I advise to disrupt yourself before something or somebody else does.

DISRUPTION HAS BECOME PART OF OUR BUSINESS VOCABULARY

Business literature is littered with articles about, and use of the word, "disruption." There are disruptive technologies, industries, companies, and sometimes even nations. Typically, the disrupters are the game changers, usually for the better and to their profit. Disruption isn't about change writ small. It is about big, attention-grabbing, smack–you-upside-the-head change. It can be revolutionary, but one thing is certain: The disrupted are never the same.

THE BENEFITS OF SELF-DISRUPTION

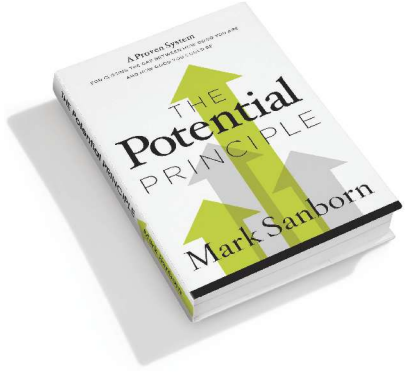
Rather than waiting to be disrupted by outside forces, what happens when you choose to disrupt yourself? Self-disruption can benefit us greatly. It can keep us moving forward and improving. It can prevent complacency and assure growth. But to benefit from it the most, we need to choose it rather than have it thrust upon us.

I doubt you started the day hoping to be disrupted. Most people don't. Despite its many benefits, disruption is unsettling at best and unpleasant at worst. That is especially the case when someone or somebody else disrupts us.

Most people and companies wait for disruption to change them. They respond and call it change management. In reality, they have no other recourse. They are simply taking the change forced upon them and adapting or even tweaking it for survival. And you can't count on returning to your former level of success once you have been disrupted from outside.

Think about someone on your team who has become complacent. What is your responsibility as a leader? Likely you need to disrupt them and their nonproductive routine. To allow something to continue is to inadvertently condone it. Too often leaders are unwilling to disrupt others, not because of the discomfort it will cause that person, but because of the discomfort it causes them as a leader.

As a leader, you need to regularly ask yourself, "Who or what needs disrupted?"



Welcome to the

BIOSIMILAR WORKFLOW REVOLUTION

Get to market faster with personalized workflows

The path of a biosimilar to market is unpredictable. This is why we created innovative workflows built for fast and confident decision making and a global support network that will partner with you to create customized solutions that address your unique challenges.

Pharma Starts with **You**

Learn more about how we can support your biosimilars program at bio-rad.com/info/LSL

BIO-RAD

Brilliant discoveries. Delivered.

We are Patheon, and we bring to bear 40 years of experience and expertise, from development to manufacturing. We also bring global reach. An industry reputation for being right on time, the first time. Supply chain solutions designed to simplify complexity and speed up the process. And a passionate belief that together we can make the world a healthier place.

Patheon®

A HEALTHIER WORLD. DELIVERED.