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How Novo Nordisk Turned Adversity Into

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How Novo Nordisk Turned Adversity Into Opportunity

p. 16

JESPER HØILAND
President of Novo Nordisk Inc. USA

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Biopharma — Beware Of The Activist Investor

ROB WRIGHT Chief Editor

Activist investors and hedge fund managers seem to take a general view that the business of business is business. Let's consider an example just outside of our industry.

Since consumer food giant Mondelez International was spun off from Kraft Foods in 2012, shareholders have notched a total return of about 68 percent, 13 points above the S&P 500, and 16 points above its industry peers. But that success hasn't stopped hedge fund managers turned activist investors (e.g., Nelson Peltz and Bill Ackman) from acquiring a significant stake in the company and then proceeding to push for even higher profits. While their meddling may result in greater returns, what will be the true cost of that success? Mondelez CEO Irene Rosenfeld says that addressing the concerns of just two activist investors consumes one-quarter of her time and has resulted in her requesting a new executive to assume some of her duties so she has more time to deal with activist-related issues. But while these activist investors play "corporate fantasy budget football" with a Fortune 100 business, one has to wonder how long before their cost-cutting initiatives result in decreased productivity, employee burnout, higher turnover, lower product quality, or product recalls. As outsiders we might not get overly concerned about a bad batch of Oreos or Ritz Crackers, but what if an activist investor took a shining to your biopharmaceutical company? Doesn't the prospect of activist meddling that leads to a shortage of life-sustaining medications seem a bit more serious? And while you might think Big Pharma immune to such a scenario, consider this: If Mondelez International were a biopharma, it would be bigger than Gilead, Amgen, AbbVie, Lilly, Bristol-Myers Squibb, Biogen, and Celgene.

As you field questions from investors who unabashedly maintain the mantra of being in the business of shareholder profit and not helping the sick, keep in mind the importance of ethical decision making. For what will be the consequences should more investors such as Martin Shkreli and Kyle Bass decide they want to play biopharma CEO for a day? Although activist investors can be good at bringing new ideas to the table, potentially lifting value and holding leadership accountable, they also can be extremely fickle. Just ask David Pyott, former president and CEO of Allergan, who is featured in our article on page 20. In fact, like Irene Rosenfeld, Pyott, too, has had the pleasure of having to deal with Bill Ackman, who partnered with Valeant Pharmaceuticals in a hostile takeover attempt of Allergan back in 2014. When I asked Pyott what was one of the biggest lessons he learned during the tumultuous time period that he refers to as "seven-and-a-half months of total war," he said, "Fortune smiles on the well-prepared."

Pyott's "been there, done that" when it comes to dealing with activist investors. His insights are especially appropriate this month with the BIO CEO & Investor Conference as a backdrop and the hundreds of biopharma executives knocking on doors in search of funding.

So, if you're an executive trying to make your biotech dream — one that helps those less fortunate while still providing a reasonable return — come true, don't underestimate the importance of being prepared for the kind of investor who is focused *only* on profits. Because though the business of biopharma needs to be *about* business, it also needs to be about something more, and much better than that represented by the likes of Martin Shkreli.

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Q Will CRISPR deliver on the promise to transform the field of biology – why or why not?

A IN THE LABORATORY, CRISPR OR GENE EDITING has proven to be a highly useful tool in genome analyses and engineering such as the creation of model organisms and studying diseases such as cancer that result from multiple mutations. In humans, CRISPR certainly has the potential to cure some genetic diseases. Some of the challenges currently faced include the fact that the editing may not be 100% or that there could be off-target effects. In addition, CRISPR has the same challenges that are faced by the RNAi field. This centers around targeting the system to specific cells/tissues. If the genetic change required is only in one organ or only in very specific cell types (e.g., hematopoetic stem cells), this could be more difficult. Significant progress has been made over time in the RNAi (RNA interference) field, for example, in liver targeting. There are numerous academic research groups and biotech companies worldwide who are using CRISPR, the field will certainly advance, and as a result, many of these challenges could be solved.

LAURA HALES, PH.D.
has nearly 20 years of industry experience, the bulk of which as a biologics discovery researcher. She is a founder of Extend Biosciences and The Isis Group.

Q What are your top books on leadership and why?

A DRIVING AND LEADING THROUGH CHANGE are critical leadership capabilities. Some of my current favorite books include:

- *Influencer, The New Science of Leading Change*: Find vital behaviors that drive change, measure, and influence to motivate for changed behaviors.
- *Execution, The Discipline of Getting Things Done*: Establish beliefs to influence behaviors directly linked to goals.
- *Leading the Lean Enterprise Transformation*: Transform through Lean and Six Sigma to make room for efficient growth.
- *Nobody Ever Gets Credit for Fixing Problems that Never Happened: Creating and Sustaining Process Improvement*: Working smarter trumps working harder long-term.
- *The Leadership Pipeline, How to Build the Leadership Powered Company*: Cultivate change in leaders transitioning to new roles.
- *Positivity*: Foster heartfelt positivity to increase openness to new possibilities.
- *7 habits of Highly Effective People*: My periodic "go-to" for reflection and reinvigoration of personal change; a perfect refresher to start the New Year.

CHARLENE BANARD
is SVP of global quality and technical operations at Shire Pharmaceutical and is accountable for global GMP and GDP quality functions.

Q What low-cost initiatives could help improve clinical trials?

A ALL ASPECTS OF CLINICAL TRIALS REQUIRE MAJOR CHANGE: design, recruitment, execution, and reporting of the results. Deficiencies in all of these contribute to the disastrous state of clinical research. Improving the design of clinical studies is a relatively low-cost initiative that would increase the quality of clinical research and make biopharma R&D more productive. Three areas to be addressed:

1. Publishing detailed results of all trials will result in fewer "nonstarter" trials that chase a target or patient population already adequately tested.
2. Leverage advances in computer sciences to analyze existing data from all available sources, and implement in silico models.
3. Give a major voice in "shaping up" clinical protocols to end users: patients and physicians.

All of the above have been talked and written about. There is general agreement of their potential, but there are precious few efforts to implement these changes.

TOMASZ SABLINSKI, M.D., PH.D.
is cofounder and CEO of Transparency Life Sciences.

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WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Symic Biomedical is in early development with several drug candidates uniquely targeting the extracellular matrix (ECM), the biological scaffold upon which cells migrate, proliferate, differentiate, and survive, and which also affects cellular behavior in specific tissues. The company's current pipeline focuses on two main areas, vascular injury and osteoarthritis (OA), in that order, with its lead candidate currently in a Phase 1-2 PoC (proof-of-concept) trial in peripheral artery disease (PAD). For OA, its lead candidate is a synthetic bioconjugate that is injected into knee cartilage to bolster its structure and remove the cause of related pain.

WHAT'S AT STAKE

Almost all drugs target some process or mechanism that occurs inside cells, the building blocks of life. But there is more to tissue than those living bricks — the mortar that holds them together; namely, the ECM. But the ECM is more than mortar. It is dynamic as well as structural, directing cell division and distribution and determining the function and even appearance of tissues. "Cells have an interactive relationship with the extracellular matrix," says Symic CEO Ken Horne.

The ECM consists of water, minerals, fibrous proteins, and "proteoglycans" — each one consisting of long, carbohydrate-related molecular chains or "glycosaminoglycans" attached to a protein core. When a tissue sustains a wound, even in the most sterile conditions, the ECM triggers a set of appropriate responses, such as coagulation or inflammation, leading to healing. Often, though, the response itself causes damage such as scarring. A common example is injury to the skin, but the same principle applies to the inside of blood vessels. Even the most competent angioplasty, bypass surgery, or renal dialysis leaves injured tissue in its wake.

Symic's lead drug candidate, SB-030, is a biotherapeutic injected during vascular procedures. It mimics natural proteoglycans that attenuate the biological response to vascular injury, mainly scarring and thrombosis, by binding to the ECM and shielding platelets from exposure to the injury. In choosing the starting point for human trials of SB-030, PoC was the top criterion, Horne says. "The PAD indication is probably not where we'll end up commercially. It is just a great trial to demonstrate this technology." PAD has the advantages of being well-studied, with well-developed preclinical models, but still no effective treatment.

As the second area of focus, OA would be a huge step up in market size for Symic and undoubtedly require a large marketing partner. "OA is an indolent, smoldering, chronic disease," says Horne. "It will never really go away. Nonetheless, it is a Holy Grail. There is nothing available for it, and nothing else in development clinically has our target profile — to affect both the structure, which is the cartilage, and the symptom, which is the pain."

Symic's ECM technology was developed at Purdue University, beginning in 2008. Two of the Ph.D. students involved eventually became cofounders of the company, along with their professor. They migrated to California and, wisely realizing they needed an experienced business hand to run the company, found and recruited Horne, a former VC who had already sold his first startup. Symic is now moving from its original home, the UCSF (University of California, San Francisco) QB3 Incubator, to a dedicated facility and has been fairly successful at fundraising for its stage of development. But Horne makes it clear the company has no so-called exit plan. "I cringe at The White Knight fallacy: 'We'll build to this point and get acquired right there.' If you're going to build something, build it to be self-sustaining. That is the vision for Symic."

KEN HORNE
CEO

Vital Statistics

16
Employees

Headquarters
San Francisco

Finances

Total raised:
$43M
(Series A, A2)

Lead investors:
Lilly Ventures
Nordic Bioscience
Mitsui Global
Ally Bridge
Alexandria Real Estate

Research partnership funding

Nordic Bioscience, clinical collaboration for osteoarthritis program (terms not disclosed)

Latest Updates

October 2015:
first patient enrolled in SHIELD (shock inhibition evaluation with azimilide) study in peripheral artery disease

November 2015:
$25M Series A2 closed

December 2015:
U.S. patent issued (9,217,016) covering OA candidate, SB-061

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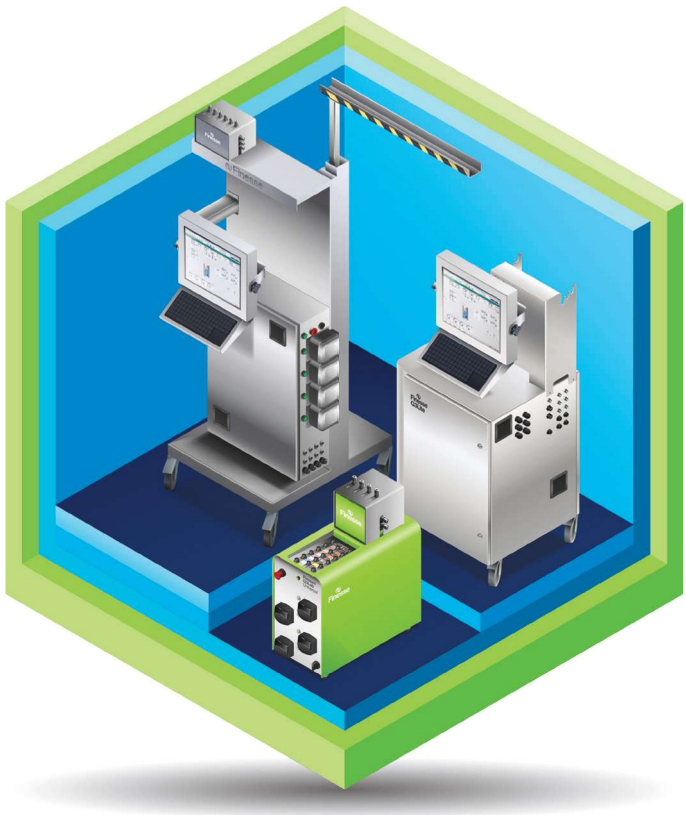

ObamaCare On The Precipice

JOHN McMANUS The McManus Group

Congress opened the 2016 session by finally getting a bill that repeals large swaths of ObamaCare to the president's desk. It took numerous attempts over the past several years, but some parliamentary maneuvering enabled the Senate — the primary roadblock — to repeal the Medicaid expansion, subsidized insurance exchanges, and a host of ObamaCare taxes through a process called Budget Reconciliation. The bill left the substantial Medicare cuts in place and therefore was scored as saving $516 billion over 10 years. President Obama promptly vetoed the legislation (only his eighth in seven years), but the effort clearly delineated Republican intentions to scrap the law should they win the White House this year.

Since enactment of ObamaCare, Republicans have vowed to "repeal and replace" the law. What has happened to the "replace" part of the "repeal and replace" of ObamaCare? We are told that is forthcoming. But the Republican caucus has had difficulty forging consensus, because any serious attempt will likely require them to either advance similar policies they just repealed (e.g., refundable tax credits for insurance) or open them to withering criticism of taking away coverage Americans have come to depend on. Providing coverage generally requires spending a lot of taxpayer dollars. Conservatives do not want to be accused of voting for new spending and entitlements, but moderates fear a backlash should individuals lose their coverage. What to do?

Fortunately, there is no reason to delay targeted changes until a comprehensive replacement can be achieved. Congress made a first swipe late last year when it successfully:

- eliminated the requirement for states to change the small-group market definition from 50 to 100 employees, thereby lowering health costs for small businesses by 18 percent
- suspended the medical device 2.3 percent excise tax for two years
- delayed imposition of the 40 percent excise tax on "Cadillac" health plans for two years
- suspended the tax on insurance plans for one year.

Noticeably absent in the end-of-year tax package was any relief for the pharmaceutical industry, which did not even request that its $3 billion to $4 billion annual fee be rescinded or suspended. With the public fixated on pharmaceutical pricing, the industry is in a more defensive posture and kept its head down as other sectors furiously lobbied for relief.

PROSPECTS FOR FURTHER TARGETED FIXES IN 2016

This year, it may become more difficult to legislate as the elections loom and there are very few legislative days to move bills. But Congress has the opportunity to build on last year's targeted improvements in the same way it made changes in 2015 by building bipartisan support to amend the more onerous aspects of the law.

One example is relief small businesses are seeking for absurdly punitive fines for doing right by their employees. Pressure is building from small businesses to rescind a $100 per day, per employee penalty for providing "health reimbursement arrangements" to employees, whereby employers provide pretax resources for employees to purchase coverage on the individual market. Many small employers who could not afford to buy coverage were using these arrangements to help their employees finance premiums in the individual market or cover out-of-pocket health costs. In 2014, contributions to HRAs averaged about $1,390 for individuals and $2,781 for families.

The Treasury Department opined that this cash assistance constitutes employer-provided insurance and is in violation of ObamaCare mandates. The penalties became effective on July 1, 2015, and most small businesses do not even know they may be in violation and subject to massive penalties for trying to assist their employees. A business with four employees — e.g., a hair salon, small home builder, bicycle repair shop — could be subject to fines of $146,000 ($36,500 per employee) for providing healthcare assistance in the wrong way. That could be a business-ending event for a firm that is not required to provide any coverage at

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all; the employer mandate only applies to businesses with more than 50 employees.

The National Federation of Independent Business, National Association of Self-Employed, the National Manufacturers Association, and other groups are now mobilizing on Capitol Hill to build bipartisan support for legislation to repeal those penalties and permit these arrangements. More than 70 Republicans and Democrats, equally divided, have cosponsored Reps. Boustany (R-LA) and Thompson's (D-CA) Small Business Health Care Relief Act, and bipartisan support is building for Sens. Grassley (R-IA) and Heitkamp's (D-ND) companion legislation in the Senate.

COLLAPSE UNDER ITS OWN WEIGHT?

Advocates of an outright repeal of ObamaCare may be heartened by indications that the health insurance market is becoming increasingly unstable and may collapse under its own weight.

Recently, the Obama administration announced that 11.3 million Americans had signed up for its health exchange plans. That's better than the administration's conservative estimate of 10 million earlier last year, but far below the 21 million the Congressional Budget Office had projected when the law was enacted six years ago. More troubling is the demographics of those who are enrolling — they tend to be older and sicker and thus more costly for the insurers participating. Nearly half of those enrolled in 2016 are older than 45, and the coveted demographic of individuals under 30 signed in smaller numbers this year as compared to last year despite higher individual mandate penalties, which are also known as "taxes" according to the Supreme Court.

Part of the problem is the exorbitant deductibles, which make the coverage useless to anyone expecting modest health costs. According to HealthPocket, the average deductible for a "silver" or midtier plan in 2016 is $3,117 for an individual and $6,480 for a family.

But pushing more of the cost onto enrollees has not abated premium growth for covered services. Premiums for silver plans rose by about 10 percent in 2016, according to the Kaiser Family Foundation. A more comprehensive view of premiums across all plans — bronze, silver, gold, and platinum — by the Daily Caller Foundation found that premiums increased by a whopping 20.3 percent. This could lead to a death spiral over time where healthier enrollees drop out of the pool and can no longer cross-subsidize the sicker enrollees who consume far more healthcare than their premiums can offset.

Hastening the death march, the left's experiment with not-for-profit healthcare has been a total bust. Fourteen of ObamaCare's 16 nonprofit co-ops, which were created to provide an alternative to for-profit insurers, have become insolvent, costing the federal government $1.4 billion and causing 800,000 individuals to seek healthcare elsewhere. These dumped co-op enrollees may find themselves with fewer alternatives as UnitedHealth, the nation's largest insurer, recently threatened to exit the ObamaCare exchanges. And many other plans are taking losses for underpricing plans, which ObamaCare's risk corridors cannot cover.

Compounding these concerns is the sheer operational complexity of the program, which may end up canceling coverage for even the subsidized individuals who find it useful. The Internal Revenue Service reported in January that about 1.4 million households that received subsidies for their ObamaCare plans failed to properly account for that assistance on their tax returns, putting their subsidies at risk if they want to retain their coverage.

The architects of ObamaCare decided to provide subsidies through the tax code so they could argue they had delivered middle class tax relief, but many subsidy-eligible individuals had little or no tax liability, so they were provided "refundable" tax credits that could be advanced to their chosen insurer and immediately reduce the cost of their premium. The average subsidy-eligible individual received a subsidy of $300 a month, which covered roughly three-fourths of the cost of the premium.

"Noticeably absent in the end-of-year tax package was any relief for the pharmaceutical industry, which did not even request that its $3 billion to $4 billion annual fee be rescinded or suspended."

Individuals are supposed to account for those credits on their tax returns in the following year. Those who fail to do so cannot get them in advance, making health insurance unaffordable to them. Nearly 1 million households failed to file the new form that accounts for the subsidies, which was introduced in the 2015 tax season. Another 316,000 households that received the credits failed to file any tax return at all. And 150,000 requested extensions but never followed through. All told, nearly one-third of the 4.6 million subsidy-eligible individuals could potentially lose their tax credits. Expect the Obama administration to refrain from enforcing this provision. But how would a new administration handle this issue, particularly one intent on eviscerating the program?

Good question. But at this stage of the campaign we have little insight into who will occupy the Oval Office.

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.

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HOW NOVO NORDISK'S U.S. PRESIDENT TURNED ADVERSITY INTO OPPORTUNITY | By R. Wright

JESPER HØILAND
President of Novo Nordisk

How Novo Nordisk's U.S. President Turned Adversity Into Opportunity

ROB WRIGHT Chief Editor @RFWrightLSL

Less than two weeks into Jesper Høiland's new role as president of Novo Nordisk Inc. USA, the unthinkable happened. "Four-thousand colleagues and I were in Denmark as part of a company celebration," he recalls. "While on this trip, I learned that we [Novo Nordisk USA] had just lost access to the commercial plan of one of our most important U.S. business partners, Express Scripts [ESI]." A $104+ billion pharmacy benefit management (PBM) company covering nearly 45 million people in the U.S., Express Scripts had accounted for between 15 to 20 percent of sales for Novo Nordisk's soon-to-be blockbuster, Victoza (a once daily injection to treat type-2 diabetes).

On Sept. 3, 2013, that all changed when the largest U.S. PBM decided to not only exclude Victoza from its formulary, but also Novo's top-selling modern insulin, NovoRapid. Høiland had arrived in the U.S. with a tough task — grow a business unit already contributing 46 percent to Novo Nordisk's annual global sales of $14.8 billion. Now, however, he faced a much more difficult prospect — preventing the Express Script decision from torpedoing Novo Nordisk's flagship business. Under Høiland's watch, not only has Novo Nordisk USA survived the Express Scripts debacle, it has thrived, accounting for 48.5 percent of the company's global sales.

Finding New Ways To Grow In The Midst Of Crisis

Høiland was still in the very early phases of aligning team expectations when the company lost the ESI business. "I was so new that I had to figure out what ESI stood for, what a PBM was all about, and what market access meant to our business opportunities," he says. "In situations like this, you have to get the lingo down. So, you have to be willing to slow down and ask what the various acronyms stand for, so everyone is on the same page."

Finding his to-do list quickly getting larger, Høiland knew he had to place an immense amount of trust in his team to help navigate Novo Nordisk through this difficult time. Having been a management consultant, his first approach was to consider the typical cost-cutting measures (e.g., layoffs) that accompany such a loss in business. But he quickly realized that wasn't the approach to take. "Instead of me determining where we should cut, we assembled a team to conduct a cost-saving exercise," he explains. Since he was still new, he delegated the task of picking the people for this new team to U.S. senior leaders and members of the executive team. This was not only a practical decision, it also helped show that he had trust in his leadership team.

Twenty-five people were chosen for the new team, and each was assigned from five to seven tasks related to identifying how the company was spending money. Once areas of cost-savings and their corresponding amounts were determined, the team members were faced with another task. "We didn't just ask them where to cut," Høiland explains. "We asked them where they thought the money that was just saved could be better used. So, it was not a cost-cutting exercise. It was more about having an organization that continues to grow organically by finding new ways, in new circumstances, to do so."

The Importance Of Fostering Internal Communications

Høiland says that one of the keys to getting through the ESI — and any business — crisis was not to let it shape him, but instead, to empower his team to shape the crisis itself. That's just one of the leadership philosophies he's discerned during his 26-year tenure at Novo Nordisk. Another one of his favorites is, "When your back is against the wall, it is tough to see the writing on the wall." That's why he's not the type of executive who spends his days in long meetings or a lot of time sitting behind his desk. Instead, he's often moving around the building instead of waiting for people to

How Exercise Can Help A Leader's Mind

"I get a kick out of going to the office on my bicycle and enjoying that free ride," says Jesper Høiland, in reference to his Princeton, NJ, commute. The president of Novo Nordisk Inc. USA says he gets ideas out of expelling energy. "That's what I like about exercise," he states. "It takes just a few minutes for you to stop thinking about your business. Then, as your endorphins start to kick in, you find yourself focusing on something else, and before you know it, you become more creative in your thinking."

But Høiland doesn't just bicycle as a means to exercise his mind; it also fulfills a purpose. This past October, Høiland and a group of other NJ area riders were training for the JDRF Ride To Cure Diabetes, in Death Valley, CA. "We rode 105 miles in the warmest place on earth to raise over $50,000 for JDRF," he says. In preparing for this grueling test, Høiland really pushed hard to have the energy he thought he would need. "As soon as the sun was up, I was on the bike to the office," he shares. Upon arrival, as well as at the end of the day before heading home, he would do some additional training. "Spending three or four hours a day exercising is not my normal routine," he attests. "But my boss [CEO Lars Rebien Sørensen, a nine-year JDRF Death Valley Race participant] asked me to participate." According to Høiland, riding in the Death Valley charitable race was on his bucket list of things he wanted to accomplish this year. "And when you commit yourself, you follow through, not come up with a bunch of bad excuses."

Høiland's approach to preparing for the JDRF race reminded me of his style as a leader. For example, when confronted with the Express Scripts decision to exclude Victoza and NovoRapid from its U.S. formulary back in 2013, Høiland didn't go about assigning a bunch of cost-cutting busy work. Instead, his approach was to have the team conduct purpose-driven exercises. "It's not just cost-cutting, but figuring out how we can reallocate the resources where we saw opportunities," he states. "We stood together through the crisis, and this is why the organization is still here and growing."

come find him. "When I come to the office on my bicycle, and I meet people in my sweaty outfit while walking the corridors, that can be one of the best ways to find out things," he states. "If people are not afraid of you, they'll be more willing to tell you what they think."

Even during a crisis, Høiland allocates 30 to 40 percent of his time to being outside of his office, which includes working with sales representatives in the field. To get a real feel for what is happening in his organization, he believes in working with a broad cross section of field salespeople. When he goes to POAs (plans of action), he tries to meet as many of the sales team as possible so he can set up his own field ride-alongs, which he's done in more than 60 countries.

"My approach is to make sure that I'm not just known by the management team around me," he says. "Leadership by walking around is probably in any Management 101 textbook. But it's not so easy to apply if you're stressed and nervous. For me, understanding what is happening on the front lines, figuring how we can improve, and what it is we need to do gives me the energy I need to energize and motivate the organization as a whole."

Part of that understanding comes from another strategy Høiland has employed since taking over at the 1,500+ employee office in Plainsboro, NJ. He regularly invites employees to his office to talk about issues they are concerned about or topics he's interested in. Sometimes the employees are chosen at random, and sometimes he hand-selects them if there is a particular topic he knows he wants to get their opinion on. "I tend to just shut up and listen to their views," he states. "Not everything has to relate to a crisis. For example, one of the items high on my agenda is how we can make our employees healthier." (See sidebar "Healthy Employees = Healthy Company.")

Where To Focus Beyond Employees

Høiland obviously makes it a point to focus on employees. However, he credits having gone through the financial crisis caused by the loss of the Express Scripts contract for pushing him into the arms of the customer — the patient. Of course, most pharma companies these days are touting their patient-centricity programs or initiatives. Høiland acknowledges the importance of such initiatives, but cautions that "being patient-centric, for example, still means you should be smart about executing your patient-assistance programs."

He explains that when he first arrived in his new position, he was frustrated when he looked at the numbers pertaining to the patient-assistance programs. "I found out that, although a lot of patients were being helped by getting our products for free, the distributor was taking millions of dollars for distributing these products." In fact, two-thirds of executing the patient-assistance programs revolved around the cost of the drugs' distribution. He was adamant they find a way to reduce that expense "not because I wanted to be stingy or didn't understand the U.S. environment, but simply because I wanted to allocate the money to where it makes most sense — for even more patient-assistance programs," he attests.

One of the initiatives Høiland worked on with the Danish government and foreign ministry was to find ways to eliminate the types of tenfold price increases that sometimes occur in countries like Africa. "It was called the base of the pyramid," he recalls. "The idea came from a book

I read, *Fortune at the Bottom of the Pyramid, Eradicating Poverty Through Profits*, by C.K. Prahlad. In a country like Kenya, we ended up making a deal with the government where we provided our product at a fixed price, so you couldn't change the price offering that we made, and neither could the country's middlemen. As a result, we ended up distributing a product for a very reasonable price." To Høiland, this experience was not only a good example of what it means to be patient-centric, but served as the inspiration behind the decision to revamp the company's U.S. patient-assistance programs to be more cost-efficient.

Høiland concluded our conversation by commenting on how businesses deal with crisis. "In these situations, you need to identify the issues and figure out how to challenge the company's employees to transform the business into something new. That's what leadership should be doing." L

Healthy Employees = Healthy Company

NovoHealth is Novo Nordisk's worldwide employee health program that seeks to create a workplace culture that promotes and supports healthy living. The idea is that healthy employees equal fewer people taking sick days and, in turn, a healthy company. Jesper Høiland recounts how, when he first came to the U.S. office, he noticed that it was expensive to buy a salad in the company cafeteria. "If you're a healthcare company, truly focused on the health of your employees, doesn't it make sense that all the healthy food on campus should be supported by the company and be almost free of charge?" he says. That experience led to the company reducing the pricing on all healthy food sold at the cafeteria. A similar change occurred at the on-site fitness center, which was underutilized when he first arrived. After getting feedback from employees as to how the facility could be better, the decision was made to sign an agreement with a hotel that is an integrated part of the Novo Nordisk building. Now, for $10 a month, employees have access to amenities such as training, an outdoor tennis court, and a swimming pool. For those who wonder why he didn't just make it free of charge, Høiland says, "Because I want things to have a certain value; otherwise it's not going to be appreciated."

DAVID PYOTT
Former President and CEO
of Allergan

Inside A HOSTILE TAKEOVER

Lessons From The Allergan-Valeant War

ROB WRIGHT Chief Editor @RfwrightLSL

Everything was going fine for David Pyott on Monday, April 21, 2014 — until around 2:15 p.m. That's when Pyott, then president and CEO of Allergan, saw Bill Ackman, billionaire hedge fund manager and activist investor, on CNBC.

Having used the fund he founded (i.e., Pershing Square Capital Management) to quietly acquire 9.7 percent of Allergan's shares, Ackman had become the company's single largest shareholder. And now he was on TV explaining why Allergan should welcome being acquired by Valeant Pharmaceuticals International (NYSE: VRX). It was the beginning of what Pyott later would refer to as "seven-and-a-half months of total war."

The cash-and-stock transaction was valued at just under $46 billion, a figure Ackman listed as "a 38 percent premium" during his CNBC interview.

Pyott watched as Ackman used the CNBC platform to cheerlead short-term investors to buy in, while cautioning Allergan long-term shareholders that another bigger and better deal wasn't waiting in the wings.

When asked what was one of the biggest lessons he learned during this tumultuous time, Pyott responds, "Fortune smiles on the well-prepared."

WHERE DOES HOSTILE TAKEOVER PREP BEGIN?

A day after Allergan found out about Valeant's plans, the company implemented a poison pill defense; existing shareholders could buy stock at a steep discount if any single investor acquired more than 10 percent of Allergan shares. "The poison pill is always a part of being ready for a raid," Pyott explains. "You have it on the shelf and typically only use it when you need to buy time for the board to negotiate the best outcome, including agreeing to negotiate with the raiders."

Of course, most companies have a plan

in place for what to do in the event of a crisis or raid. "If you don't scenario plan at least once a year, then, frankly, you are not doing your job," states Pyott. "You should always try to go through a variety of takeover scenarios to see what crack you think raiders will try to stick a knife into and pry open." At Allergan, the board had conducted such an exercise about six months before Ackman showed up. "You implement your crisis plan, but sometimes you have to quickly formulate a new plan because during a hostile takeover, the 'war' goes in all sorts of unexpected directions."

Pyott says the key to a crisis plan is making sure you have the right processes and people to move rapidly to adapt to new unforeseen situations. The people component of that plan starts with building and maintaining a very competent board of directors. But building such a board can take a long time, which is why Allergan developed a matrix to track the experience of its directors. The matrix showed whether board members had experience/background in key categories such as pharmaceuticals (the most important), healthcare, finance, scientific, and consumer, just to name a few. "Of course names could be in multiple boxes," Pyott clarifies. "The matrix was very helpful when we were building and maintaining our board. It helped us stay focused on determining where we were the weakest."

BUYING TIME DURING A HOSTILE TAKEOVER REQUIRES LONG-TERM SHAREHOLDER BUY-IN

When activist investor and hedge fund manager Bill Ackman took to the business world television airwaves on Monday, April 21, 2014, to share his thoughts on why the acquisition of Allergan by him and Valeant (a 38 percent premium) was such a good idea, he was also planting seeds of doubt in the minds of long-term Allergan shareholders. "Word is leaking out in the market of various players who might be competitive here who said to their shareholders that they are not going to bid for the company [Allergan]," said Ackman. David Pyott, the former president and CEO of Allergan, says that when faced with such a situation, time is your friend. "Our banks were very quick to say, play a long game," he states. "It became very clear to me that because of all the tax savings, being realistic, the only company that could pay more than Valeant would be another foreign company, whether it was really foreign or inverted." But before you can find a white knight to ride in to save the day, playing a long game requires buy-in from long-term shareholders.

When you do the math, Valeant's first bid for Allergan was a $10 billion premium from the day that Ackman started buying his first shares. "Investors that wanted us to continue fighting the takeover attempt feared the stock price could go back to where it was before," Pyott relates. "Four weeks after the first time we met with investors once the hostilities began, they [investors] told us that if we didn't drive up the stock price and earnings dramatically in the short term, they'd be forced to sell." To prevent this from happening, Allergan leadership developed a profit improvement plan, which took less than seven weeks, including board approval. "We said we were going to come up with a $475 million run rate of savings by year two, and we actually did way over $500 million," he says. While R&D is the lifeblood of any biopharmaceutical company, when embroiled in a hostile takeover, you have to be willing to cut — everywhere. "R&D was hit for about 14 percent," Pyott shares. "We went right across SG&A [selling, general & administrative expenses] cutting, including some of the longer-term market building investments." Pyott analogizes the process to being able to run faster by just losing five pounds. "We were certainly motivated to lose weight to give us the time we needed to play a long game."

In addition to the profit improvement plan, Pyott began counseling Allergan's long-term-oriented stockholders to prevent their positions from falling into the hands of the raiders. "I asked them that if Valeant were to go away tomorrow, where do they think Allergan's stock price would settle after about day five. I also asked them what they thought the true value of the company was," he says.

Pyott helped coordinate the investor slide decks that were produced, focusing on why Allergan was a great independent company that was being undervalued, while also attacking Valeant. "In their deal, roughly 60 percent of the consideration would have been equity. People used to scream at me for highlighting that. But one of our highest fiduciary duties as a board on behalf of the shareholders was to point out the value of Valeant paper, because if the deal came to pass, they were going to end up owning it."

Whether your company is large or small, when a deal like the one brokered by Valeant and Ackman emerges targeting your company, Pyott says to expect an enormous rearrangement of your shareholder base. "If you lose control to the short-term-oriented shareholder base, the game is over," he relates. "The lesson is that you need to be very well-prepared for the whole investor relations outreach to keep the long-oriented shareholders from selling." For those who held out, they were well-rewarded for having done so. In November 2014, it was announced that Actavis had agreed to buy Allergan for $219 a share, trumping the Valeant and Ackman deal. But don't feel too bad for Mr. Ackman. Pyott estimates the activist investor made about $2.6 billion, thanks to his being able to find a white knight in the form of Brent Saunders, the CEO of Actavis, who was willing to pay roughly a $12 billion premium over the last clear formal Valeant/Ackman offer.

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> *"You should always try to go through a variety of takeover scenarios to see what crack you think raiders will try to stick a knife into and pry open."*
>
> **DAVID PYOTT**

That board strength came in handy when the Valiant/Ackman acquisition attempt began. At the time, the board had a lot of tenure; most members had been around for five to 15 years. Henri Termeer, the former CEO of Genzyme (and a board member for only four months prior to the takeover attempt), even had gone through his own similar saga with the sale of that company to Sanofi.

COMPETENCY REQUIRES PREPARATION AND FREQUENT COMMUNICATION

Having a competent board of directors that can work well together is always important, but especially when faced with a crisis. During the takeover time period, the board met 34 times, with only four of those being face-to-face, and almost every meeting being attended by every board member. But Pyott admits that conducting board meetings via a conference call is more difficult than in person. "When on the phone you can't see their body language, if they are frowning, smiling, or just looking downright scared," he says. "Strong rapport is critical."

"The best way to keep everyone on the same page and alleviate pressure is through frequent communication," he explains. But don't make the mistake of viewing email as an adequate substitute for frequent verbal communication. "We knew that no matter what happened, we were probably going to get sued for having sold or sold for too little," he states. "While we were extremely careful with emails, we did have some pretty major email incursions towards the middle of the summer." Bottom line for Pyott: In-person communication allows for transmitting more information, more clearly, while providing less ammo for lawyers later.

Pyott says the large number of board meetings during this time period was necessary because the company had never encountered a situation like this — a company and an activist hedge fund manager combining forces in a strategic takeover attempt. "I also didn't want to let what was being discussed in the media get too out of hand," he states. "That's why I never let more than five or six days go by without a meeting to help the board understand what was going on." Pyott started every board meeting with an introduction of what had happened in the last five days since they had previously spoken, gave his perspective, and provided an opportunity to give input. Board members were given a daily media roundup of the relative information so "we could discuss the important stuff versus the rubbish," he says. For many of the board meetings, the members could have from three to 400 pages to read prior. "After the roundup, we'd get straight into the agenda so everyone knew what my game plan was, next moves, and what I needed from them," he explains.

Some of the meetings would last only an hour or two, but sometimes they could extend to four hours or more if the board was contemplating a major deal or resetting a strategic plan that would, for example, require bank involvement to run the numbers. During the April 29, 2014, meeting, Pyott told the board he needed to spend 90 percent of his time focused on the raiders. "I asked for their approval to pass all the day-to-day management of Allergan to Doug Ingram, president, and Scott Whitcup, EVP and head of R&D," he recalls. Part of his strategy was to keep the leadership from having to deal with the press with nonoperational matters revolving around the takeover. "I was paranoid about information leaking out," he elaborates. "I also wanted to be able to monitor what the raiders were up to without the day-to-day distractions of running Allergan." The other part for wanting Ingram and Whitcup in charge was it provided Pyott the time necessary to formulate a game plan, beginning with the gathering of necessary advisors.

THE VALUE OF STRATEGIC ADVISORS

Any crisis plan should outline which advisors the board has agreed upon to use. In this situation, Pyott says they started with choosing which banks they would look to for advice. "Of course, these are people whom you've used for a lot of different work [e.g., licensing, buying] over the years," he says. "That was an easy choice for us that we had done during our first board meeting." The board chose Goldman Sachs and Merrill Lynch and also agreed to use the lawyers Allergan had used previously, Latham & Watkins. "Some really good advice that Henri Termeer gave us, having gone through his own acquisition horror, was for the board to consider having its own counsel separate from that of the corporation. So we added Wachtell Lipton, because they usually work on the defense side of things."

Two other advisors brought in by the board were services Allergan had never had the occasion to secure before: a crisis PR company and a proxy advisor. "Bringing in all of the advisors, even the last two, was done within 14 days of hostilities commencing," Pyott says. All

of the advisors were chosen based on previous experience with board members.

Pyott credits the bankers, lawyers, and PR firm with collectively giving him some very solid advice. "To avoid having people going in different directions or being unclear about deadlines or priorities, they recommended we have a daily call," he explains. On the call, they would discuss what was going on, what their response would be, and any information the PR firm was hearing from Madison Avenue and in the newsrooms. After that call, Pyott would have another call with a smaller group, including members of management (e.g., CFO, head of investor relations, general counsel, deputy general counsel, PR director) in Irvine, CA, along with about four advisors. They kept the group small to minimize the risk of leaks or email hacks, and they were careful to include only the very senior people from the advisors. Their job was then to coordinate with the rest of their firms on the outside.

In the past, it was usually Pyott, the CFO, or a member of communications who would typically deal with the press. For this crisis, though, they decided early on that Pyott would be the only person who could speak for the company regarding the takeover. The PR firm warned Pyott that he had likely never undergone the type of intense questioning he was bound to encounter from the media in the coming weeks. To help him prepare, the firm would pepper him with questions for an hour while filming his reactions. They would then review the film and repeat the process. "That was very valuable for getting me prepared to answer some of the key questions," he states.

Making Pyott the point person for any questions regarding the takeover took the pressure off the other senior leaders and ensured only one message was being conveyed. This strategy evidently paid off. "Ackman attempted to have an executive session with the lead director," Pyott says. "We obviously declined that opportunity. Their game was to try to divide and conquer and to try to get people to say things that could be very regrettable. I even remember hearing about one person who got a call on his cell phone while at home from a hedge fund manager trying to find out information."

SOMETIMES BUSINESS IS PERSONAL

David Pyott, the former president and CEO of Allergan, says people are often surprised when they learn he has never met Bill Ackman, the activist hedge fund investor who attempted to partner with Valeant in a hostile takeover attempt of Allergan. "I talked to him on the phone three times," he shares. "He was always very quick to point out that he was our largest shareholder. Our third and last phone conversation lasted about 15 minutes. For the first 10 minutes, he laid out his expectations and demands, to which I clearly did not agree. He then threatened me by stating that, if I did not follow his wishes, this would be a sorry way to end my long career. So I told him I didn't see any reason to meet until he had something completely different to tell me."

As for Valeant Pharmaceuticals CEO Michael Pearson, Pyott says the last time he spoke to him was in April 2014. "Out of principle, I will never speak to him," he shares. "The last phone call was merely to reiterate what had been stated in writing publically a few days before. After that, he only transmitted formal acquisition proposals to me by email after a press release had already been issued. He, too, had nothing to add beyond his written statements. I abhorred his business model and principles."

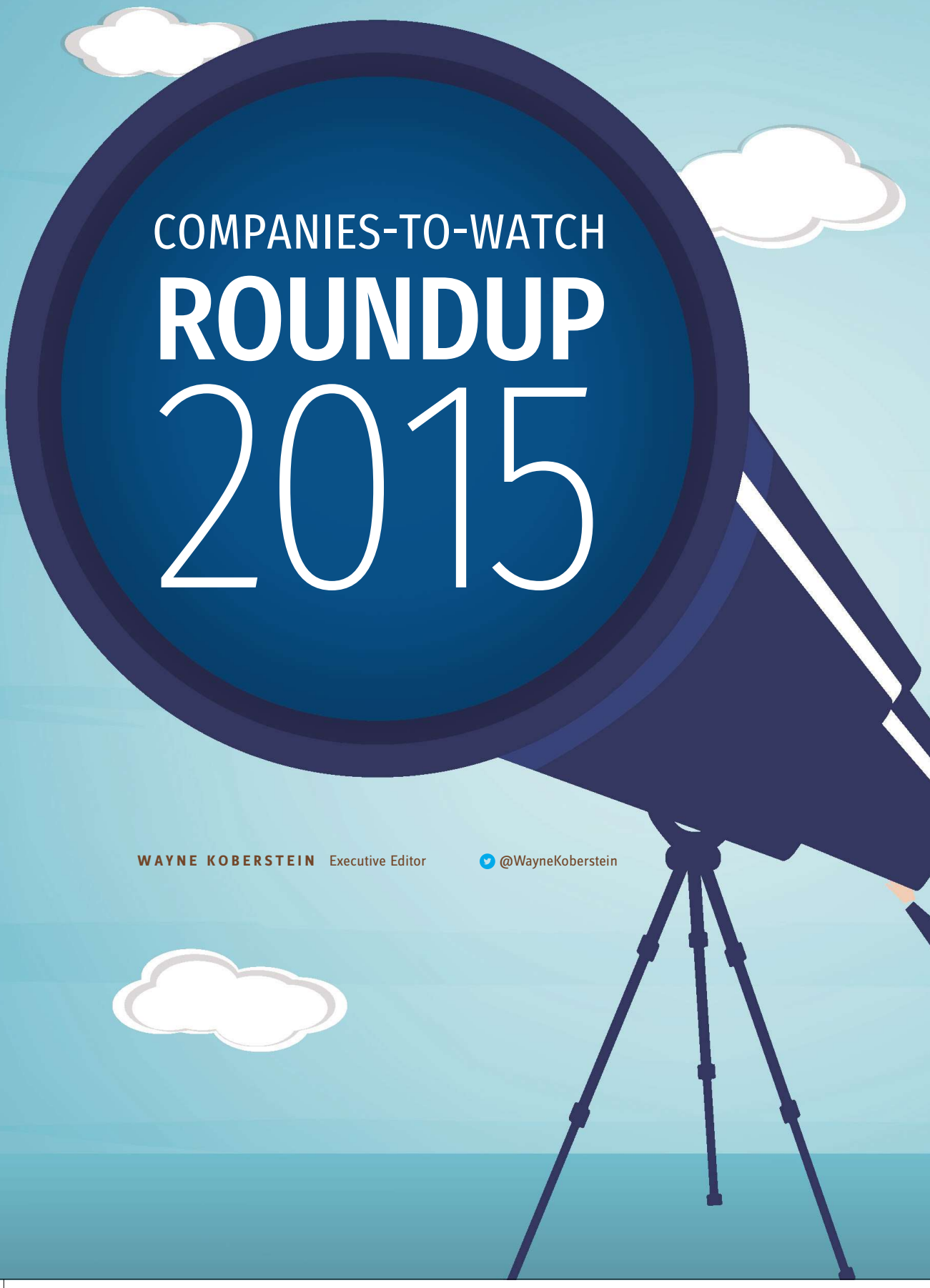
While some of his standoffishness may appear to be Pyott taking the hostile takeover attempt a bit personal, the reality is limiting his access to Ackman and Pearson was also part of his strategy. "They got me pretty pissed off a couple of times," he admits. "But you can never lose your cool when you are in front of the TV camera or being caught by the press." Instead, Pyott sought to find ways to turn Ackman and Pearson against one another. "I tried to cause some major consternation between those two," he reflects. "Ackman had a different goal in terms of encouraging Pearson to pay a higher price, because for him it was all about the money. I think they started screaming at each about four weeks into the whole process, based on comments from third parties dealing with both of them. I must admit that I used to derive some pleasure from that."

ACHIEVING GROWTH DESPITE BUSINESS CHAOS

One of the keys Pyott credits with successfully staving off the Valeant and Ackman takeover attempt was splitting the team in two — one to deal with the raiders and one to run the daily business of Allergan. "I told Ingram and the operational leaders that I didn't want them getting distracted, so they would be used very selectively at the boardroom level, often only for explaining any deals we might be looking at ourselves," he says. "I warned them that there was probably going to be a lot of garbage in the press, but not to believe it all, and certainly not to spend their workdays reading it, because then we would surely fail."

Pyott empowered Ingram and the operational leadership team to keep the business moving ahead and to make decisions on their own without his input. "I told them that if anything was slowing them down, whether it be somebody not cooperating or just some really difficult decision, then obviously they would be able to get 20 minutes with me. But otherwise, I made sure they knew they had my full mandate to just get it done." As time went on, Pyott says he spent less and less time with the leadership team. "They did such a great job," he recalls. "It was pretty amazing that we had the best operating year in our history, growing the company revenues 17 percent while under attack."

COMPANIES-TO-WATCH ROUNDUP 2015



WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Unlike the companies profiled in our Companies-to-Watch (CtW) section in prior years, the 2015 crowd made mostly scientific rather than financial news. There were no record-breaking IPOs or stock peaks that produced the majority of headlines in the general or investment-oriented trade presses. The general tone was, thus, reassuring rather than sensational.

Almost without exception, the 11 CtW of 2015 (January – November) made subsequent progress in or toward clinical development of their lead products after appearing in the column. Most of the companies have passed early proof-of-concept studies and started new trials in humans to test their drug candidates for safety and effectiveness.

Still, the particular stories of the companies selected for CtW in 2015 continue to resonate with a number of overarching themes that have both immediate and long-term significance for the industry. Among those are drug pricing, global health threats, age-related diseases, vaccination and antibiotic resistance, pain treatment, and of course, the efforts to address multiple unmet and often unnoticed areas of medical need. For this year's Companies-to-Watch Roundup, we asked companies not only to update us on their progress since their CtW coverage, but also to describe their targeted goals and milestones for 2016. In this Roundup, we also note some recent headline-grabbing developments with some of our CtW of previous years. (See the sidebar, "Ripped from the Headlines.")

JANUARY

PaxVax

A socially responsible company pushes for global affordability and practical access to its "third-world" vaccines.

"2015 was an exciting year for PaxVax, marked by the expansion of our commercial operations globally, pipeline progress, and significant financial investment that position us for growth in 2016."

Nima Farzan
CEO

In April, we announced the signing of a series of new commercial partnerships and distribution agreements for our commercial typhoid vaccine Vivotif. These agreements ensure the global availability of Vivotif across Europe and Australia and complement our growing direct sales and marketing capabilities in the United States. Vivotif is currently licensed for

sale in 25 countries.

In early December 2015, we closed a $105M financing deal led by Cerberus Capital Management, which allows us to eliminate debt and focus on the execution of our business plan, including the growth of the Vivotif business and launching our lead pipeline candidate Vaxchora, a single-dose oral vaccine for cholera.

Also in December, we announced the FDA's acceptance of our BLA (biologic license application) for Vaxchora. As part of this acceptance, Vaxchora was granted priority review status, a critical step in the process of being awarded a priority review voucher. The BLA, which was submitted on Oct. 16, 2015, is based on successful results from 10- and 90-day cholera challenge trials, as well as two other safety and immunogenicity trials in healthy adults.

I became CEO of PaxVax in May 2015, succeeding company cofounder Ken Kelley. Ken's vision for a company that has both a social and commercial mission has been an important catalyst in our success to date.

In 2016, we will be focused on executing our strategy to build the world's largest specialty vaccine company; making progress on our pipeline candidates, which include vaccines for anthrax, HIV, and hepatitis A; the expansion of our Vivotif business globally; and preparing for the commercial launch of Vaxchora. The FDA's action date for the Vaxchora BLA is June 15, 2016. If licensed, Vaxchora would be the only vaccine available in the U.S. against cholera.

FEBRUARY

Tetra Discovery Partners

A determined young company revisits a discarded mechanism and finds a new path to broad-based therapeutics for cognition-related diseases such as Alzheimer's.

"Tetra achieved the goal of entering BPN14770 into human clinical trials. BPN14770 is a first-in-class Phosphodiesterase 4D Negative Allosteric Modulator (PDE4D-NAM), with the unique potential to both improve memory and slow progression of Alzheimer's disease. Research has shown that PDE4D modulates the formation of new synaptic connections between neurons, and plays a key role in learning and memory storage. Studies are planned later in 2016 to assess the cognitive benefit of BPN14770 in otherwise healthy elderly subjects with cognitive decline."

Mark Gurney
Chairman & CEO

MARCH

NeuroPhage Pharmaceuticals

A company targeting a common amyloid structure of misfolded proteins in neurodegenerative diseases such as Alzheimer's and Parkinson's — and perhaps many others.

"The key event for NeuroPhage during 2015 was the acceptance of the IND (investigational new drug application) for its GAIM fusion protein, envisioned as a broad-spectrum disease-modifier, applicable to a variety of neurodegenerative disorders. First-in-man dosing will begin during the first quarter of 2016, and we anticipate near-term financing news as well."

Richard Fisher
Chief Scientific Officer

APRIL

Resverlogix

This 14-year-old company patiently stacks up clinical evidence of health benefits gained from oral treatments with a new, epigenetic MOA (mechanism of action) for long-neglected, large-market chronic diseases.

"Resverlogix has made significant advances with the clinical program since April 2015. In Q4 2015, Resverlogix commenced a Phase 3 clinical trial, BETonMACE, with lead drug apabetalone (RVX-208) in high-risk patients with coronary artery disease (CAD) and Type 2 diabetes mellitus (DM). The primary outcome measure will assess the effect of apabetalone on time to first occurrence of major adverse cardiovascular events (MACE) in high-risk Type 2 DM patients with CAD. In the primary outcome measure, MACE is defined as a single composite endpoint of cardiovascular death, or nonfatal myocardial infarction (MI), or stroke."

Donald J. McCaffrey
President and CEO

In other 2015 significant news, Resverlogix:

- licensed RVX-208 China rights to Shenzhen Hepalink Pharmaceutical Co., Ltd. (Hepalink); estimated sales milestones and licensing royalties could exceed $400 million
- closed a $50 million private placement deal with Hepalink and Eastern Capital Limited
- received two patents for apabetalone in China
- presented new data detailing positive effects of apabetalone in CAD, chronic kidney disease, reduction of alkaline phosphatase (ALP) and beneficial effects of apabetalone on glucose metabolism
- announced the commencement of an orphan disease program specific for complement mediated diseases.

Upcoming milestones for Resverlogix in 2016 will include:

- commencement of a proof-of-concept pilot trial with apabetalone in the complement mediated disease Paroxysmal Nocturnal Hemoglobinuria (PNH)

BIOCOM

Biocom serves Southern California's life science community, a region offering the perfect climate for life science innovation and future innovators because of its uniquely collaborative spirit, high concentration of world-class research institutions and its strong foundation for new company creation and development. Biocom provides a tremendous range of initiatives and programs in public policy, capital development, group savings, professional network building and talent development. With over 750 members, **we are Biocom Strong.**

- commencement of a proof-of-concept pilot trial with apabetalone in the kidney-related diseases
- announcement of a second regional licensing deal.

MAY

AvidBiotics

This company's "precision" drugs may hold the key to defeating antibiotics resistance and collateral harm to the microbiome — plus a new approach in antivirals and immuno-oncology.

"AvidBiotics' emerging protein engineering-based MicAbody platform has matured to enable the rapid design, production, and testing of multiple proteins, each of which engages both the innate and adaptive immune systems to precisely attack and kill targeted cancer cells in vitro and in vivo. The MicAbody proteins effectively pre-arm NKG2D-bearing cells with bispecific molecules to create virtual CAR-cells. We expect this year to select and advance specific MicAbody candidates toward the clinic with partners. Our other precision medicine platform, engineered high molecular weight bacteriocins (Avidocin proteins) to kill targeted pathogenic bacteria, has advanced and can now kill the most virulent strains of the C. difficile bacteria. We showed their ability to prevent infections in mice colonized by C. difficile and exposed to antibiotics, a model of the most frequent bacterial infection in U.S. hospitals. Treatment of healthy mice with Avidocins also has been shown not to compromise the ability of the healthy gut microbiota to resist infection by other bacterial pathogens, as do antibiotics. We anticipate in 2016 to advance the Avidocin manufacturing processes and broaden the killing spectrum of Avidocins to protect against the vast majority of C. difficile strains that are the scourge of American hospitals."

David Martin
CEO

JUNE

Genkyotex

Inhibiting NOX enzymes back to normal levels may forestall the ravages of reactive oxygen species in multiple diseases.

"In September 2015, Genkyotex announced top-line data from the Phase 2 clinical trial with GKT831, our lead NOX1&4 inhibitor. In patients with diabetic kidney disease, GKT831 demonstrated an excellent safety profile and statistically significant reduction in both liver enzyme and inflammatory marker levels. Treatment with GKT831 for 12 weeks resulted in fewer adverse events than placebo, confirming its excellent safety profile. However, a reduction in albuminuria, the primary efficacy endpoint of the trial, was not achieved in this patient population within this time frame."

Elias Papatheodorou
Acting CEO

The data from the Phase 2 trial confirmed preclinical data obtained in multiple models of fibrotic disorders, providing the clinical foundation for the development of GKT831 in the treatment of nonalcoholic steatohepatitis, systemic sclerosis, and idiopathic pulmonary fibrosis. The company is currently finalizing Phase 2 study designs, which are expected to begin in 2016.

GKT771, a potent and highly selective NOX1 inhibitor has been validated as a clinical candidate. GKT771 has broad therapeutic potential in multiple inflam-

RIPPED FROM THE HEADLINES

Some of the Companies To Watch (CtW) featured in prior years made major waves in 2015.

- **IN DECEMBER, KALOBIOS** — freshly acquired and headed by Turing's Martin Shkreli — announced it would buy benznidazole, a drug for the treatment of Chagas Disease from Savant HWP (CtW May 2014). Since then, Shkreli's professional and legal troubles have put the benznidazole deal in doubt.
- **ALSO IN DECEMBER, STEMCELLS (CtW APRIL 2013)** announced it would cut other development programs and lay off a quarter of its workforce to concentrate solely on developing its HuCNS-SC neural stem cells for spinal cord injury, based on encouraging Phase 2 results.
- **IN JANUARY 2016, CEMPRA (CtW JUNE 2013)** filed an NDA with the FDA for its new antibiotic, solithromycin, and said it would offer a sale of $175 million in common stock to fund the product's commercial launch — only to reduce the offering to only $107 million a few days later.
- **IN JANUARY 2016, SEVERAL LAW FIRMS LAUNCHED INVESTIGATIONS INTO POSSIBLE SECURITIES FRAUD BY ESPERION** (CtW September 2013) centered on conflicting statements the company allegedly made about whether the FDA would require an additional cardiovascular outcomes trial for approval of ETC-1002, the company's lead LDL-Cholesterol-lowering drug. At the JP Morgan Healthcare Conference in early January, Esperion clarified that the agency had requested a long-term safety study be "under way" at NDA approval, not that the study was required for approval.

matory and vascular disorders and will be ready to enter the clinic by the end of 2016.

JULY

Tonix Pharmaceuticals

A company focused on restorative sleep and a second pathway to pain control for PTSD and fibromyalgia.

"During the second half of 2015, Tonix completed enrollment in its Phase 2 'AtEase' clinical trial for TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in the treatment of posttraumatic stress disorder (PTSD) and completed enrollment in its Phase 2 clinical trial for its drug TNX-201 (dexisometheptene mucate) in episodic tension-type headache (ETTH). Tonix also signed a cooperative research and development agreement (CRADA) with the U.S. Army Medical Materiel Development Activity (USAMMDA) to explore expansion and potential development of TNX-102 SL for the treatment of military-related PTSD. Additionally, we presented significant differences from placebo in our completed Phase 2b BESTFIT clinical study of Tonmya for the treatment of fibromyalgia. Looking to the remainder of 2016, we expect to report top-line data for our clinical programs in fibromyalgia, PTSD, and ETTH."

Seth Lederman
CEO

AUGUST

Thrasos Therapeutics

A company using a novel mechanism in an obscure but nonsolitary space to prevent acute kidney injury and treat chronic kidney disease.

Thrasos did not return a response to our request for an update — and everything has remained equally quiet for the company since last fall. In November, it extended its intellectual property protection in Japan, where it won a composition-of-matter patent for its lead product, THR-184, a peptide drug for prevention of acute kidney injury (AKI) in cardiac-surgery patients. Our CtW column on Thrasos emphasized the often-overlooked importance of kidney damage as a common side effect of many other conditions and treatments, including surgery. According to the company press release regarding the Japan decision, THR-184 has similar patent coverage in the United States, Australia, and many countries in Europe such as England, France, Germany, Italy, and Spain. "This patent covers a genus of polypeptides, including THR-184, and the use of these peptides to treat subjects having, for example, kidney disease. The allowed claims also cover nucleic acids, vectors, and cells comprising the nucleic acids that encode the allowed peptides," says the company.

SEPTEMBER

Corbus Pharmaceuticals

A company intent on flipping the "off" switch in rare, chronic inflammatory diseases.

Corbus also did not send an update for this article, though it recently shared the following information with us. All three of the company's drug-development programs for its lead candidate Resunab are now in midstage clinical trials. In September, the company started a Phase 2 trial of the drug for treatment of cystic fibrosis (CF), adding to its ongoing Phase 2 trials in systemic sclerosis and dermatomyositis, which began earlier in 2015. "Resunab is a first-in-class drug that induces the resolution of inflammation. The CF study is our third Phase 2 trial launched so far this year in a rare inflammatory disease, joining the Phase 2 trials in systemic sclerosis and dermatomyositis launched previously in 2015," said Yuval Cohen, Ph.D., CEO in the press release announcing the CF trial. "The systemic sclerosis and CF studies are scheduled to conclude in the fourth quarter of 2016, and we look forward to reporting top-line data at that time."

OCTOBER

Mucosis

Needle-free, mucosal vaccines that trigger a two-fisted immune response offer a first hope for fighting RSV (respiratory syncytial virus) — and raising the bar in vax technology.

"Mucosis Chief Scientific Officer Kees Leenhouts, Ph.D., published an article in ADVANCE for Respiratory Care & Sleep Medicine *about how advances in knowledge of the immune system are providing hope for an RSV vaccine. Mucosis also presented insights on development of a novel needle-free vaccine for RSV prevention at the RSV Vaccines for the World conference in November. The presentation highlighted the antigenic and immunological characteristics of the company's unique prefusion F antigen, the core technology behind its lead product, RSV vaccine SynGEM. In 2016, the company will be entering human proof-of-concept studies for SynGEM and looks forward to sharing more data as it moves toward a viable solution to prevent this devastating disease. In the coming year, Mucosis also plans to continue pursuing additional partnership opportunities with industry, nonprofits, and academia in order to fully exploit its novel Mimopath vaccine technology."*

Tom Johnston
CEO

NOVEMBER

Vascular Pharmaceuticals

Tackling diabetic nephropathy through a new pathway is the focus of this company.

"Vascular Pharmaceuticals' Phase 2 adaptive design clinical program continues to progress, and enrollment of an additional patient cohort began in January 2016. A financing round to support the next phase of enrollment closed in December 2015. The next interim data analysis will occur in Q4 2016."

Richard J. Shea
CEO (L)

Assessing The Discovery Outsourced Services Market

STELLA STERGIOPOULOS, MICHAEL WILKINSON, JOSEPHINE AWATIN, AND KEN GETZ

In 2012, the Tufts Center for the Study of Drug Development (Tufts CSDD) estimated that the total market for outsourced R&D services in the United States ranged from $32.9 billion to $39.5 billion, with the two most mature markets; chemistry, manufacturing, and controls (CMC) and clinical research; accounting for 44 percent of the total. Applied research (i.e., discovery) and nonclinical research — more nascent outsourcing markets — accounted for 32 percent of the total market.

Traditionally, market analysts have focused on CMC and clinical research services outsourcing due to the relatively high number of publicly held companies operating within these sectors. Estimating the size of the contract services market for drug discovery activities has been more challenging. The high proportion of small, privately held companies as well as differences in market definitions and modeling approaches have created inconsistencies and variations in market size estimates. Some market size reports focus only on services provided by CROs, while others include the technologies required for assays.

Another possible explanation for these differences in market size estimates is that market analysts have focused predominantly on the most mature activities (i.e., regularly outsourced activities such as drug toxicity assays and high-throughput screening [HTS]). More nascent services, such as assays specific to ion channels and transporters (ICT), may not be included in all market estimates, even though these niche areas have seen growth in the last few years (e.g., Lilly's joint venture with RaQualia Pharma, CRL's acquisition of Biofocus and Chantest, Pfizer's spin-off of Icagen).

As the demand for outsourcing across the entire drug development value chain continues to increase, more precise estimates of emerging areas, such as outsourcing ICT research in discovery, are required. These more accurate metrics will aid sponsor companies in strategic planning and resource planning.

STUDY METHODOLOGY

In early 2015, Tufts CSDD estimated the overall market for contract discovery

FIGURE 1

Primary, Secondary, High-Throughput Screening, and Ion Channel and Transporters Services

PRIMARY SCREENING

- Activity-Based Assays
- Automated Patch Clamp (APC)/ Electrophysiology
- Cell and Cell-Based Assays
- Fluorometric Imaging Plate Reader (FLIPR)
- Fragment Screening
- High-Content Screening
- High-Throughput Screening
- Hit Finding Biology/Chemistry
- Ion Channels
- Label Free Technologies
- Lead ID
- Lead Seeking Libraries
- Leads/Targets
- Library Chemistry
- Mass Spectrometry
- Micro Plate Reader
- Microarray Analysis
- MicroRNA (miRNA)
- Nano Mass Spectroscopy
- Proteomics
- Proteomics Microarrays
- Radioactive Flux Assays
- Real Time PCR
- Short Hairpins RNAs
- Small Interfering RNA (siRNA)
- Ultra-High Throughput Screening

SECONDARY SCREENING

- Activity Based Assays
- Atomic Absorption
- Cell Assays
- Cell-Based Assays
- Efficacy In Vitro
- Efficacy Testing
- Ion Channels
- Label-Free Technologies
- Metabolism (Metabolite ID and Production)
- Microarray Analysis
- MicroRNA (miRNA)
- Nuclear Magnetic Resonance
- Proteomics
- Proteomics Microarrays
- Radioactive Flux Assays
- Real Time PCR
- Short Hairpins RNAs
- Small Interfering RNA (siRNA)
- Transporters

HIGH THROUGHPUT SCREENING

- Activity Based Assays
- Atomic Absorption
- Automated Patch Clamp (APC)/ Electrophysiology
- Cell and Cell-Based Assays
- Efficacy In Vitro
- Efficacy Testing
- Flourometric Imaging Plate Reader (FLIPR)
- Fragment Screening
- High Content Screening
- High Throughput Screening
- Hit Finding Biology/Chemistry
- Ion Channels
- Label Free Technology
- Lead ID
- Lead Seeking Libraries
- Leads/Targets
- Library Chemistry
- Mass Spectrometry
- Metabolism (Metabolite ID and Productions)
- Micro Plate Reader
- Microarray Analysis
- MicroRNA (miRNA)
- Nano Mass Spectroscopy
- Nuclear Magnetic Resonance
- Proteomics
- Proteomics Microarrays
- Real Time PCR
- Radioactive Flux Assays
- Short Hairpins RNAs
- Small Interfering RNA (siRNA)
- Ultra High Throughput Screening
- Transporters

ION CHANNELS AND TRANSPORTERS

- Atomic Absorption
- Automated Patch Clamp (APC)/Electrophysiology
- Fluorometric Imaging Plate Reader (FLIPR)
- Ion Channels
- Radioactive Flux Assays
- Transporters

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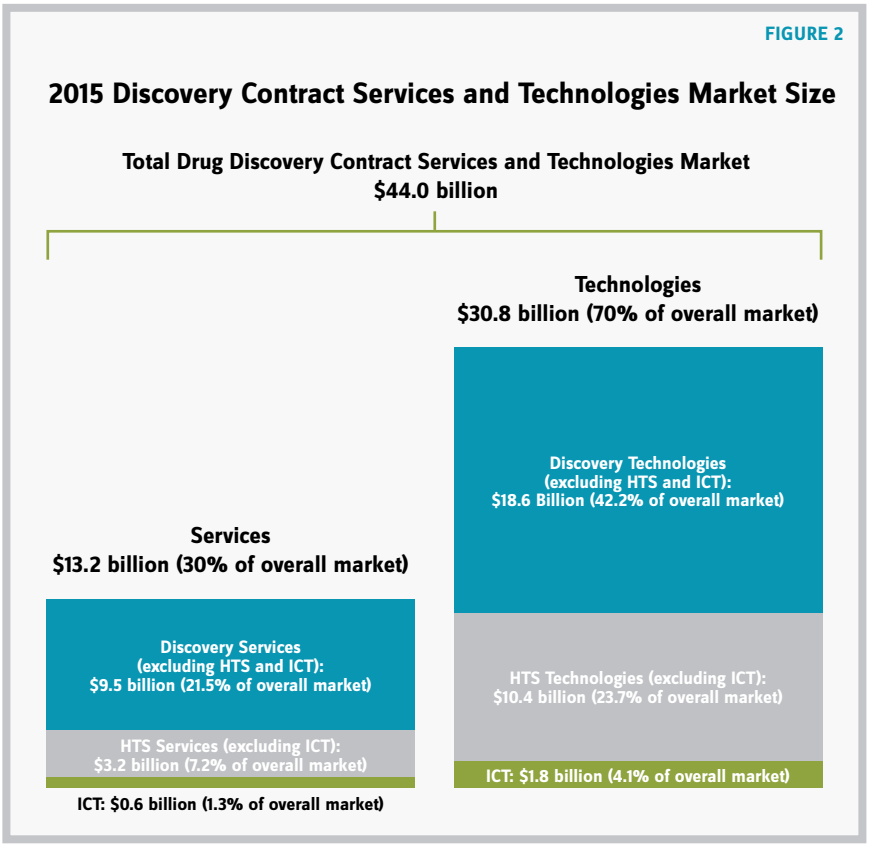
FIGURE 2



services, as well as the discovery technologies market, i.e., companies that provide technologies to biopharmaceutical companies. Tufts CSDD used a bottom-up approach to assess the markets for discovery activities, HTS services, and, lastly, key services within discovery such as ICT research services. The new study used the same methodology as the 2012 study but with emphasis on a more granular assessment of the discovery services market.

Tufts CSDD created a detailed definition of discovery services and technologies and then compiled a comprehensive list of service providers offering these services and technologies.

Services for HTS, primary screening, secondary screening, and ICT were also analyzed. Data was gathered on a total of 910 companies. Companies were included in the analysis if they had an active website during the study (conducted from March 2015 to November 2015). Tufts CSDD used proprietary databases, Standard and Poor's Capital IQ, and Pharmatching.com to identify companies operating within the discovery services market, specific services provided, and key company characteristics (e.g., company age, if publicly traded, revenue, profits, employee count). Companies were organized using the following definitions:

- Companies with 1-5 technologies, 1st quartile
- Companies with 6-8 technologies, 2nd quartile
- Companies with 9-12 technologies, 3rd quartile
- Companies with more than 12 technologies, 4th quartile

In instances when profit, revenue, and head count values were available, Tufts CSDD evenly distributed them across all the services and technologies offered by the company. Segment revenue was used for publicly held companies when possible. Once data was gathered, total discovery services and technologies market sizes were estimated, along with key financial indicators, to assess the maturity of these services and technologies.

STUDY RESULTS

In total, 910 companies offering discovery services or technologies were identified. These companies generated $44 billion in discovery services and technologies in 2015. Discovery technologies generated approximately $30.8 billion, while discovery services generated approximately $13.2 billion.

Of the 910 companies identified, 795 of them provided discovery services, while 607 of them provided key technologies necessary for discovery research (some companies provide both technologies and services).

The majority of discovery technologies and services companies are privately held; only 8.5 percent are publicly traded. The majority (54 percent) also have headquarters that are located in the United States. The following are some key differentiators between discovery services and technologies:

Discovery Technologies Companies

- ICT technology accounts for approximately 4 percent of the discovery technologies market, with HTS technology accounting for slightly over 23 percent. The rest of the discovery technologies market is made up of other technologies.
- Discovery technology companies employ 47 more individuals, on average, than discovery services companies.
- The discovery technologies market is saturated, with 86.8 percent of

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FIGURE 3

Discovery Market Defining Characteristics

910 companies identified
Generated $440 billion in 2015 | 8.5% public | 54% in USA | Average age: 18.6 years

Market	Revenues ($ billions)	Total Companies	Estimated Employees	Mean Revenue Per Company ($ millions)	Mean Revenue Per Employee	Mean Employee Per Company	Percentage Revenue Generated by Top 10 Companies
Services	$13.2	795	111,579	$16.6	$118	140	44.6%
Technologies	$30.8	607	113,458	$30.8	$272	187	86.8%
Total Discovery Market	**$44.0**	**910 (unique)**	**225,037**	**$48.5**	**$196**	**248**	**66.8%**

revenue coming from the top 10 revenue-generating companies.

Discovery Services Companies

- ICT research accounts for approximately 1 percent of the discovery services market, with the rest of HTS services accounting for approximately 7 percent. The remainder of the discovery services market is made up of other services.
- The discovery services market is nascent, with 44.6 percent of revenue generated coming from the top 10 revenue-generating companies.

The HTS market (combining services and technologies) has similar trends, with approximately 9 percent of companies being publicly held and 55 percent of companies having headquarters in the United States. Of the 910 companies identified, 629 either provide HTS services or technologies or reagents necessary for HTS.

- The average age of these companies is 18.9 years.
- The typical HTS services and technologies company generates $25.4 million and employs 120 individuals (as compared with the average 248 employees at discovery services and technologies companies).
- The HTS market is saturated, with 73.2 percent of revenue being generated by the top 10 companies.
- Of the 910 companies identified, 538 provide HTS services specifically, generating a total of $3.8 billion (including ICT). These service-specific companies generate, on average, $7 million per company and employ 57 individuals.

Focusing on select HTS technologies and services combined, ICT services and technologies generated the largest revenue followed by the broad category of cell-based assays. In contrast, more companies (244) provide cell-based assay services and technologies as compared with ICT research services (54) and ICT research services or technologies (61). Those companies that provide cell-based assay services employ an average of 26 individuals and generate $3.4 million per company.

Within ICT there were a number of mature segments: only six companies were identified as providing radioactive flux solutions (services and technologies), with all of these companies being publicly held. Companies providing radioactive flux solutions are also the oldest, on average 40.5 years old, followed by companies providing fluorescence-based ion flux assays (Fluorescence Imaging Plate Reader) services and technologies (on average 30.5 years old). Companies providing radioactive flux solutions generated $470 million in revenue, and companies providing automated patch clamp services and technologies generated $409 million in revenue.

DIFFERENCES FROM THE 2012 STUDY

This follow-on study to the Tufts CSDD 2012 initial outsourcing market size focuses specifically on discovery services and technologies.

Overall, the discovery services market is not as mature as the discovery technologies market. Additionally, the services market is more fragmented, with more

companies offering services, and the top 10 companies accounting for nearly 50 percent of the revenue generated (as compared with discovery technologies, where the top 10 companies account for close to 90 percent).

These estimates are higher than the initial 2012 Tufts CSDD report due to differences in methodology. The initial 2012 report focused exclusively on key geographic biopharmaceutical hubs in the United States, and measured productivity of each facility located in those hubs. Moreover, this analysis included companies that offer discovery technologies, whereas the 2012 analysis did not include these companies. Although the imputation methods between the two studies are consistent, the inclusion of high-revenue-generating technologies companies has likely increased the median revenue applied to companies with no revenue information.

STUDY LIMITATIONS

There are a number of limitations to this study that should be noted. Tufts CSDD relied on data from Standard & Poor's Capital IQ database to assess the financial health of privately held companies. This data is gathered using qualitative methods that may understate and overstate actual financials. Additionally, using imputed data to estimate revenue specific to a service or technology may be biased, as the smallest company's revenue may be inflated and the largest company's revenue and employee size may be deflated. Although Tufts CSDD applied a methodology that used companies of similar size with actual revenue and employee counts to impute this data for privately held companies, this bias may exist.

Future Tufts CSDD research will focus on key discovery services, looking to understand in more detail best practices for sourcing research related to ion channel and transporters due to the increase in merger and acquisition activity specific to this service. In addition, Tufts CSDD plans to analyze the data by geography to assess the economic impact of these services and technologies locally.

FIGURE 4

Validating the 2015 Early Discovery Contract Services Market

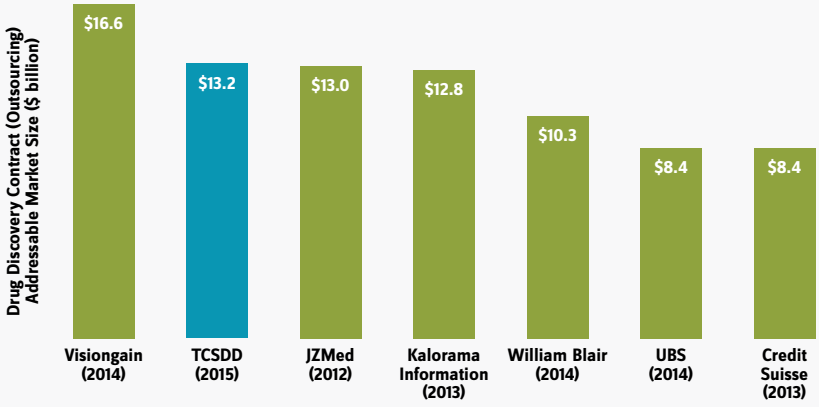
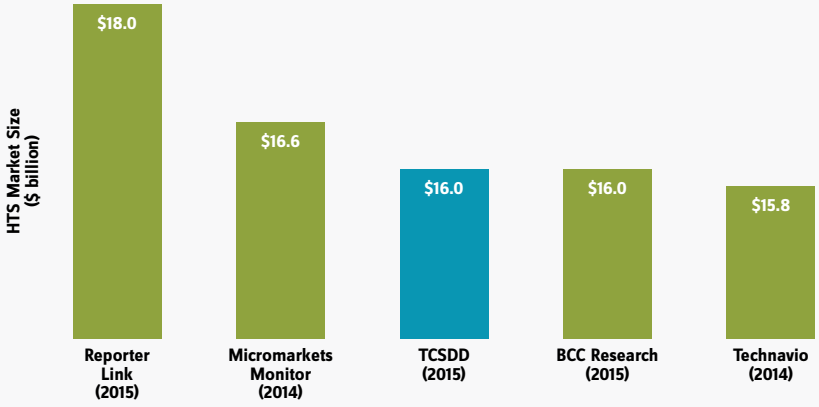


FIGURE 5

Validating the 2015 High-Throughput Screening (HTS) Market



Note: Outsourcing Addressable Market Size for 2015 when data is available. TCSDD estimate includes technologies and services.

With rising drug costs and more pressure from regulators to provide transparency on drug pricing algorithms, the use of CROs to streamline development costs will continue to grow. It is hoped that the results of this study will provide estimates for the discovery outsourcing market and aid biopharmaceutical companies in their strategic planning and sourcing decisions.

Stella Stergiopoulos is senior project manager at Tufts CSDD. Michael Wilkinson and Josephine Awatin are both research analysts at Tufts CSDD. Ken Getz is associate professor and director of sponsored research programs at Tufts CSDD.

The authors would like to thank Richie Cunningham, CEO and president, Icagen; Douglas Krafte, CSO, Icagen; and Krista Steger, president and cofounder, Forge 4ward, for their contributions to this manuscript. This study was sponsored with an unrestricted grant from Icagen (formerly XRPro Sciences).

Otsuka Alters Study Paradigms
To Prepare Sites For Clinical Success

ED MISETA Executive Editor @EdClinical

Leesa Gentry has conducted many clinical trials in her 20+ years in pharma, half of which have been with Otsuka Pharmaceutical Co. While every study is challenging in one way or another, a recent trial tested her ability to coordinate with sites to ensure they were properly equipped and trained to pull off a study.

Gentry, who currently serves as director of Global Clinical Management for Otsuka Novel Products, is accountable for the implementation of multiple global trials for products relating to MDR-TB (multidrug-resistant tuberculosis), imaging, and oncology.

Otsuka has been working on new TB medicines for over 30 years and is now the largest private funder of TB drug development in the world. As such, the majority of Gentry's time has been spent working on trials for MDR-TB, defined by its resistance to two main drugs currently used to treat TB — isoniazid (INH) and rifampicin (RMP). Patients can become resistant to these drugs if they are not administered correctly or are not given with the appropriate companion drugs.

When launching a new Phase 3 trial for MDR-TB, Otsuka wanted to recruit as many global patients as possible. Sites were set up in South America, Asia, Southeast Asia, and in the Baltic countries in Europe. Patients were even recruited in the U.S. and Egypt. South Africa was originally not included due to concerns over patients co-infected with HIV, but was included in later studies.

LOW RESOURCE SETTINGS POSE CHALLENGES

Although Otsuka had patients on almost every continent, the facilities that existed varied greatly from one location to the next. In fact, Gentry uses the term "low resource settings" to refer to what existed in many areas.

"Low resource settings are really denoted by inconsistent access to international healthcare standards in that region," notes Gentry. "Patients may experience stock-outs of medication or the country might be utilizing some sort of global granted funds to procure second-line drugs. The facilities may lack necessary infrastructure or be located in areas where transportation, electricity, or other essential services are difficult to maintain. Many of the facilities will oftentimes have fewer personnel as well. They have trained personnel at the site, but they don't have extra personnel available to perform clinical trial work on top of the daily tasks they are already required to perform."

In some locations Gentry notes there is limited access to specific types of equipment. For example, in the MDR-TB trial, Otsuka wanted to be able to compare data across several different regions. An automated system would be used to check sputum from patients' lungs to see if bacteria were growing. Many of the sites did not have the equipment necessary to do so.

With the extensive experience Otsuka has in TB, Gentry knew before the trials started that the company would be working in low resource settings. As a result, a highly qualified team was put together consisting of individuals with medical or epidemiologic experience working in this field, in MDR-TB, or perhaps at the CDC or other global organizations.

Gentry knew it would be important to have individuals managing the study that understood the resource environments Otsuka would be working in. Therefore, she included individuals who could understand what would be

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required to get all of those sites up to applicable standards. Since each site was very different in terms of infrastructure, a very individualized approach was used. "There were certainly similar themes across several of the regions," she says. "For example, we knew these sites were doing really good work, but they were resource strapped, especially in terms of highly trained staff. In many locations, we had to add staff and train them on trial requirements. There was also a lot of equipment that had to be purchased, particularly in the lab, but that was different in every case and often depended on the region."

The trial required eight or more in-patient treatments simultaneously, making it a bit more cumbersome than some previous MDR-TB studies. While some regions were used to that kind of regimen, there were many that were not. In a few areas, Otsuka actually had to create a site where patients could be treated for 56 days in more of a hospital-type setting.

SITE VISITS WERE MANDATORY

Otsuka enrolled 481 patients across approximately 20 sites. "We tried to focus on sites that had demonstrated good treatment in the past and had access to quantified, eligible patients," says Gentry. "For that reason, we deliberately tried to limit the number of sites that would be treating patients."

Since it was impossible to determine exactly what the equipment and infrastructure needs were at each site, Gentry and her team took the time to visit each one. She believes one of the most valuable lessons learned from the trial was the amount of time and face-to-face interaction required by her team.

"It was really unheard of in any trial I had worked on previously," she says. "We just decided that, in order to make this work, we were going to have to ensure our team was extremely well-connected to each site. This was accomplished by having team members make multiple visits to each site. We did use CRO partners and also hired local clinicians in each of the regions where we worked. To ensure everything flowed smoothly, we created a paradigm where those individuals worked as a part of our team. At the same time, our employees working on the project were just as involved locally as any of the CROs. At one point we attempted to track our flight miles and found that five members on our team could have gone to the moon and back. That's a lot of travel."

> *"[The face time required by site staff] was really unheard of in any trial I had worked on previously."*
>
> **LEESA GENTRY**
> Director of Global Clinical Management,
> Otsuka Novel Products

At the beginning of the study, the team included just Gentry and a medical monitor. Later, Otsuka created a position referred to as regional lead and added three CRAs (clinical research associates) to the team. Each one was put in charge of a different region and had local CRO personnel working under them. An internal SOP required the team to perform 5 percent oversight of all sites, which was later increased to 20 percent. That equated to someone having to be at the site about every other month. To ensure everyone on the team was on the same page, the initiation visit, which generally takes around four hours, was extended to two or three days.

The extension of the initiation visit allowed teams to review all of the presentations that would be used for training and to ensure that clinic nurses and lab technicians received the training. To avoid confusion, a CRO team that spoke the local language was also brought in to help with the training. The additional time also afforded teams the opportunity to re-verify facilities and equipment and review a few patient charts with staff to help them identify patients who would be eligible for the trial.

FINDING AND TRAINING PERSONNEL

Even though Gentry knew from the outset that additional personnel would have to be hired at each site, finding qualified individuals was still quite difficult. An even bigger problem had to do with several of the sites (such as those in the Baltics) being government entities. At those sites, the ability to hire additional staff was very limited due to funding constraints. Otsuka resorted to having its CRO partners hire the additional staff.

The individuals hired were generally study coordinators. If there were not enough government personnel available, the company would partner with non-governmental organizations to provide qualified workers. Generally these were entry-level CRAs who were placed at the site as study coordinators. They were managed by the site staff but paid by the CRO.

It was important to Otsuka that all sites follow ICH (International Conference on Harmonization) good clinical practices (GCP). Naturally, there were some sites where Gentry knew some additional work would be required. The standards dealt with the way the site was

documenting information, which had not been performed correctly in the past.

"For example, one of our sites had a very good clinical practice and kept a logbook of the vital signs for each of their patients, but they were kept in conjunction with all the other patients," she says. "There wasn't an individual patient chart that could be reviewed by an external third-party audit. Therefore, we had to change the way they were documenting information and then train personnel on how to do it correctly."

Physicians also required some training. Gentry notes the doctors were very talented and passionate about treating TB. However, some were not used to managing and documenting adverse events as required for a clinical trial.

"These investigators deal with MDR-TB in multiple patients on a daily basis," says Gentry. "They are not necessarily thinking about whether a particular side effect is common with many of the second-line drugs. Some of these drugs can cause nausea or other symptoms more difficult to detect, such as hearing loss. The physicians were not used to documenting such things as adverse events. So, we had to provide some training."

Doctors also were accustomed to providing data in multiple formats, depending on the task. Otsuka needed to have them focus on creating a source document that would be the single place for information to be housed. Many were also not used to transcribing that information into a second location, such as an electronic data capture (EDC) system.

Reflecting back on the process, Gentry notes it was a big deal. With MDR-TB, patients have to be directly observed during dosing. This is to make sure the patients are adhering to the requirements. That process is sometimes at odds with what is required for ICH GCP, and was one of the biggest hurdles that needed to be overcome.

"I did not expect this to be an issue," she says. "Generally, the doctor is not responsible for patients maintaining their medication and taking it every day. But in a clinical trial, control of the drug is important and medication must only be dispensed to the patient who has consented. Some of these sites had to be deprogrammed from what they were used to doing regarding dispensation, documentation, and adverse-event reporting and taught how to perform tasks in a way that would meet ICH GCP requirements."

PURCHASE NEEDED EQUIPMENT

When it came to making sure every site had the equipment needed, there were a few themes that emerged, although the needs still varied by location. Appropriate infection controls (environmental controls, personal respiratory protections, and administrative controls such as limiting staff contact with infected patients) also had to be in place at each location for both the safety of the patient and to ensure patients weren't being double-infected, which would cloud the data.

Most of the equipment required was needed in the labs. Almost every site required a mycobacteria growth indicator tube (MGIT), an automated device necessary to evaluate sputum cultures while controlling for local/regional bias. In most sites, the equipment was rented. Even if a site had an MGIT, it generally wasn't large enough to analyze the large number of samples collected. In those locations, a second unit was rented. Additional lab equipment, such as refrigerated centrifuges and microscopes, were also needed at some sites.

A reliable Internet connection with sufficient capacity was required to perform the EDC requirements of the trial. To increase the Internet capacity in many locations required switching to a different service provider.

There were other various equipment needs, such as lockable storage cabinets that would hold collected samples, as well as desks and chairs in those locations that did not normally have regular CRA visits.

"Overall, I would say we were pretty lucky to find most of the equipment we needed locally," says Gentry. "Importing equipment from another country would have made the effort a lot more difficult. When it came to locating the equipment and supplies we needed, our CRO partners were extremely helpful."

COMPARABLE RESULTS ARE CRITICAL

Prior to this study, the trial sites had only ever measured results against themselves; collecting data that would be measured across multiple regions was also new to them. But comparability of data was a major goal of this study for Otsuka.

"To make sure everyone was doing this correctly, we created a standard lab manual," states Gentry. "This ensured the same procedures were followed exactly in every lab. In addition to the normal clinical monitoring that is performed, we added another layer of monitoring specifically for the lab. Lab personnel were trained in microbiology and responsible for ensuring processes were performed according to the lab manual."

The results of the trial show the efforts of Gentry and her team were worthwhile. Otsuka was able to obtain data on 421 of the 481 patients, across every site, despite the fact that patient adherence to this type of regimen is very difficult. The lab manual Otsuka developed and utilized for this study was later endorsed by the Global Laboratory Initiative of the Stop TB Partnership, providing third-party endorsement of the standard processes used in the lab. The treatment has been approved in the EU, Japan, and South Korea, with registrations and access initiatives ongoing in other countries.

"Our data was incredibly consistent," adds Gentry. "It has been analyzed many times and in many different ways, and it has always been consistent. I think that consistency, as well as patient retention, are very good measures of quality."

How Efficient Is The Toyota Production System In Biopharma?

ALAIN PRALONG

The Toyota production system (TPS) — originally designed for the automobile industry to reduce waste so companies could become economically competitive — recently has become more popular within the biopharmaceutical industry for managing the complex endeavor of new product development and manufacturing. However, there are those who would question the effectiveness of this management approach for life science executives.

I have developed successful Lean Six Sigma approaches for product development value streams (PDVS) and technical life cycle management value streams (TLCVS). In addition, I have developed, embedded, and used TPS elements, so I would like to share my experiences and highlight the benefits and limitations.

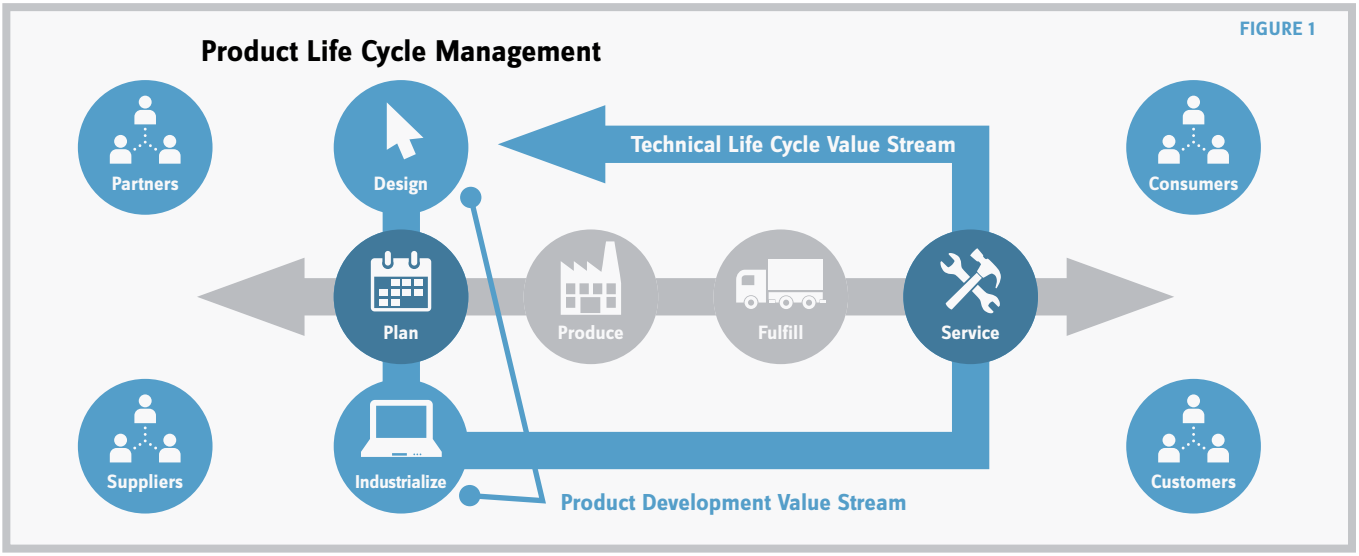
A PROCESS THAT FOSTERS BETTER DECISION MAKING

The biopharmaceutical industry is characterized by two particular hallmarks: long development times for bringing a new drug to market and long drug life cycles. For example, it takes 12 to 15 years to develop a new vaccine that then needs to be supplied to the market for decades. Both of these factors need to be taken into consideration when implementing TPS concepts in this industry. To do so, you should view product development and technical life cycle management as a continuum (see **Figure 1**). This continuum ensures reliable product supply and transfers experience from production to product development and maintenance.

A Kaizen-driven (i.e., continuous improvement) value stream organized and governed through stage gates (similar to milestones) helps all process contributors understand what to deliver, by when, and at what level of quality without major project management effort. This process fosters educated decision making regarding drug development depending on the status of the deliverables and the results at a given stage gate. Furthermore, it eliminates the risk of forgetting or not executing activities related to the required quality level since the CMC (chemistry, manufacturing, and controls) documentation is built over time instead of compiling it just before the BLA (biologics license application) submission.

The major impediments to the success of this approach include the willingness (i.e., maturity level) of the organization to respect a value stream and the organization's efforts toward compiling the documentation needed to enable educated and risk-mitigated decision making. Time, perseverance, continuity, and a first positive experience are required to motivate and persuade personnel to adhere to the principles of a TPS-inspired value stream for new product development. Embedding the PDVS, even on products in

FIGURE 1



late-stage development, has permitted identification and timely resolution of gaps that could have the potential of delaying BLA submission and product launch. **Figure 2** presents an example of how a PDVS can be organized and structured.

MOVING AWAY FROM A REACTIVE APPROACH

It's interesting to me that the biopharmaceutical industry traditionally has pursued the dogma of "the process is the product," which has resulted in a mentality of complete risk aversion coupled with more reactive rather than proactive strategies. But today's biopharmaceutical companies need to be able to identify risks and opportunities within a process and a product in a proactive way. To do so, a risk/reward matrix has to be prepared that reviews four main areas: business risk/opportunity, urgency, benefit, and cost of implementation. This new way of working establishes educated and balanced risk/reward management. Obviously, the complexity of this risk/reward matrix management is multiplied significantly with the number of different processes and products in the portfolio. Vaccine manufacturers, for example, can have over 30 marketed products. Furthermore, the risk/reward matrix needs to be continuously updated and in sync with the expectations of the regulatory authorities.

In my experience, I found developing a TLCVS with distinct stage gates to be very effective in transitioning a company to be more proactive in its thinking regarding drug development. All risks and opportunities for a given process and product are collected and then scored against an established rating system consisting of 11 questions. For each question a set of five answers is predefined to enable "answers that use the same yardstick." The outcome of the scoring creates the risk/reward matrix.

Applying the TLCVS gives you heightened awareness regarding potential risks and rewards, which, in turn, enables you to proactively mitigate/capture those risks and rewards. As for the PDVS, the major limitations reside in the maturity level of the organization. You not only have to identify risks and rewards, but also implement appropriate follow-up actions regarding your findings.

Of course, this kind of proactive risk mitigation and reward capturing comes at a certain cost. That's probably why some organizations choose to postpone proactive projects such as this in favor of saving money in the short term. But that's a dangerous strategy considering recent regulatory enforcement actions that show the cost of dealing with an average warning letter can approach $100 million.

YOU HAVE TO BE WILLING TO ADAPT

Through my work in product development and technical life cycle management, I had the chance to develop and embed TPS approaches at two biopharma companies. In the beginning of these projects, personnel were often skeptical of TPS since it originated in car and chip manufacturing. But once they witnessed its benefits, and were able to shed the mentality that "the biopharmaceutical industry is different," they became supporters of this new approach.

TPS in the biopharmaceutical industry brings product development and maintenance to a new, currently unmatched maturity level that can cope with strong pipelines and portfolios. When using TPS in the biopharmaceutical industry you have to adapt your review and intervention cycles to the requirements of drug development and maintenance. Then, the status of the deliverables for each stage gate determines management's decision-making options.

HOW BIOPHARMA SENIOR MANAGEMENT CAN BEST UTILIZE TPS ELEMENTS

In my experiences, there are certain elements of TPS that biopharma senior management find very useful. For example, dashboards that display KPIs (key performance indicators) are a TPS element that is very popular at the senior management level. Indeed, knowing the status of the different KPIs (green, amber, and red) is important for determining the overall state and performance of an organization. However, some people question if this is the right approach for decision making at the senior management level. In contrast to the TPS decision-making points, which are in sync with the stage gates of the PDVS and TLCVS, these dashboards show lagging indicators since data extraction and preparation takes significant time. Furthermore, to reduce the number of KPIs, often various parameters are absorbed and integrated, making it difficult to understand the driver for the shown performance. Often, a further specific deep-dive is required to obtain a comprehensive overview of the situation leading to an amber or red KPI. Normally, such a deep-dive

FIGURE 2

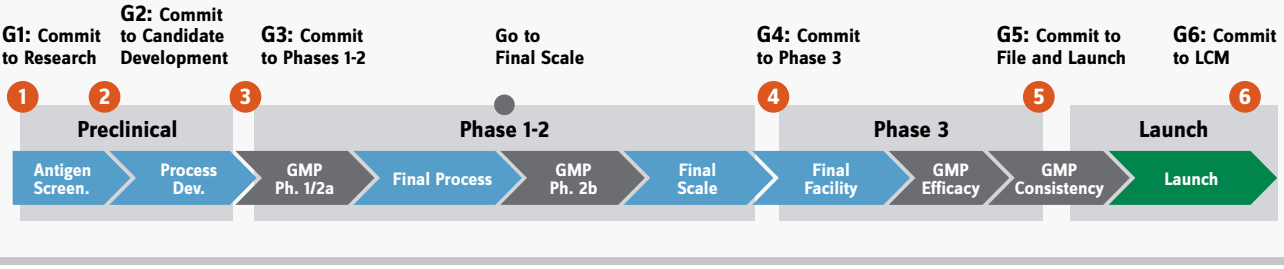


FIGURE 3a

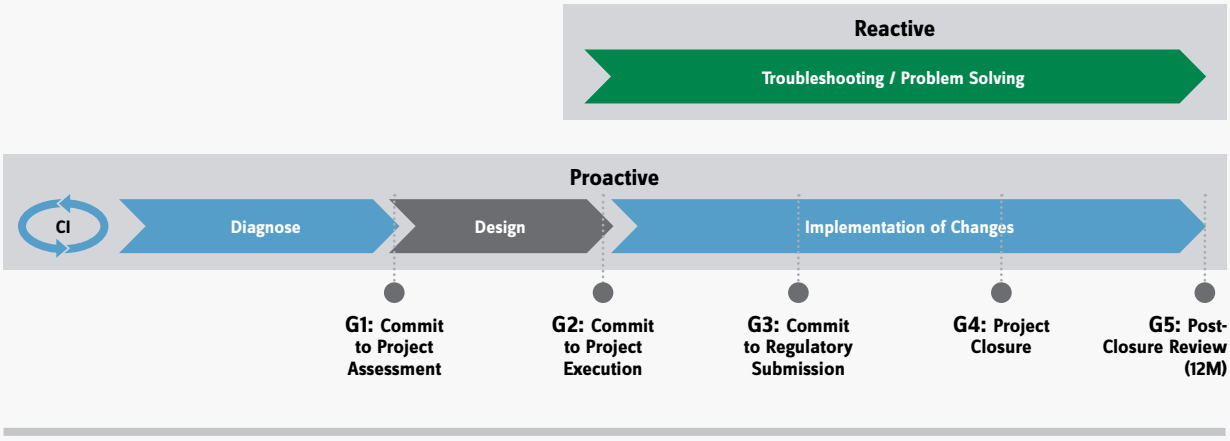


FIGURE 3b

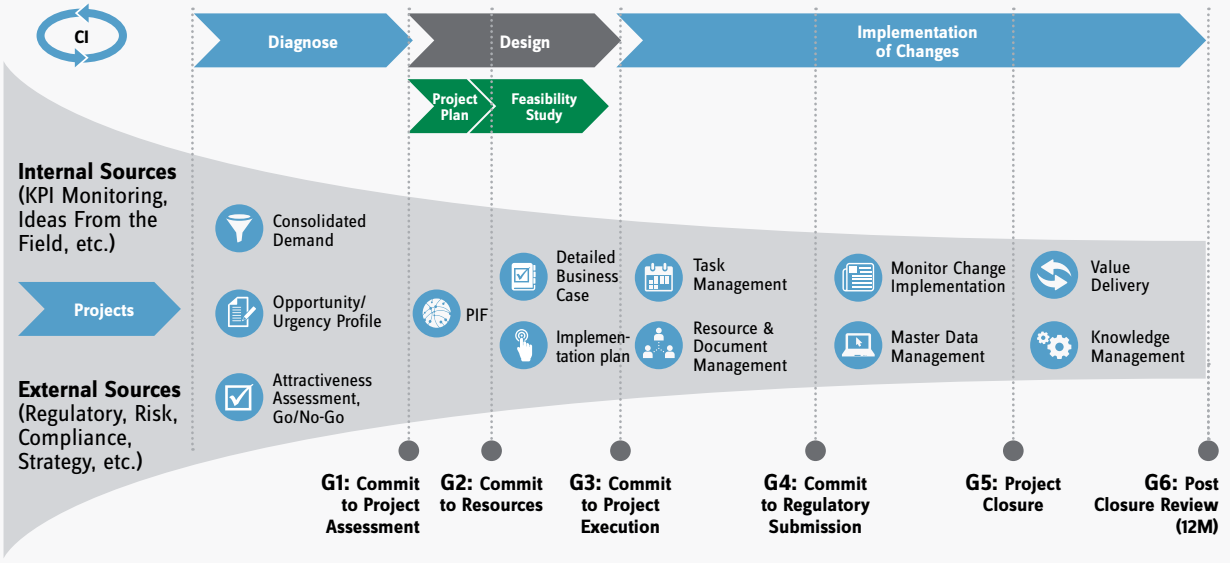


Figure 3a shows one way to structure a technical life cycle management value stream (TLCVS). One of its hallmarks is the structured approach governed by stage gates permitting shifting from fire brigade only to mainly proactive mode of operation. In the TLCVS, projects are identified and scored in the "Diagnose" step. For high-scoring projects, a project plan including various feasibility assessments is prepared in the "Design" step. Successful projects are executed during the "Implementation" step. This cycle is repeated on an annual basis and permits, therefore, establishing a continuous improvement (CI) approach for technical life cycle management that reduces the number of crises requiring reactive troubleshooting and problem solving over time. **Figure 3b** shows the 12 activities executed while running the TLCVS in sync with the stage gates.

requires another two to three months to ascertain the details. Even worse, the ability to make relevant and appropriate decisions is limited since senior management level is far away from the personnel on the shop floor creating the data used to generate the KPIs. Hence, decisions come too late or are not appropriate anymore for the evolving situation on the shop floor.

To me, there's no doubt that TPS is a useful and efficient tool for the biopharmaceutical industry. But transitioning to this more proactive way of thinking — which can be applied throughout an organization — requires a shift in the way senior management gathers and assesses its data for decision making.

Alain Pralong is CEO of Pharma-Consulting ENABLE GmbH.

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3 Keys To Successful Industry-Academic Collaborations

BENJAMIN HOFFMAN, PH.D.

Benjamin Hoffman, Ph.D., is senior director, corporate affairs at Onconova Therapeutics. One of his responsibilities is oversight of scientific academic collaborations.

Industry-academic collaborations are becoming more popular as pharmaceutical and biotechnology companies seek to harness the innovation and human capital within life sciences institutions. Both large and small companies alike engage in academic partnerships in order to expand their scientific programs in the discovery of new targets, molecules, biomarkers, and disease models. Much has been written on the structure of these partnerships — often a variety of grant mechanisms — but little attention has been paid to the successful management of collaborative relationships. The following are three suggestions for industry executives on how to align researchers and ensure maximum productivity.

1. **Share Project Management Responsibilities.** All successful partnerships require advanced identification of weaknesses, strengths, and potential synergies between the parties involved. Key industry skills include project management, budgeting, and quantification of return on investment in research. Industry programs have timelines and budgets established at the outset of each project. Most successful academics are familiar with timelines and budgets through the grant application process, and many are excellent project managers. The shared experience of project management can serve as a point of connection on all aspects of the collaboration. Identifying the primary project managers on both sides of the collaboration is a key initial step to a successful partnership. Executives should carefully consider the appointment of highly capable managers. These managers should share similar scientific values as their academic partners, have working knowledge on all technical aspects of the proposed project, and should possess strong interpersonal and communication skills.

2. **Bridge The Documentation Gap.** Project managers need to develop a shared understanding of the documentation process for the project with their academic counterparts. Although many academics document their research through note-taking, this record keeping is rarely to the standards required by industry. Thus, bridging the documentation gap is a second critical step in establishing a productive partnership. Since normal corroboration of notes may be difficult due to geographical factors, electronic lab notebooks should be employed by industry managers as a simple way to document experimental progress that also can be shared in real time.

3. **Consider Incentives And Align Success Metrics.** Next, it is critical to align success metrics between parties. Academia and industry reward systems are inherently divergent. Academics tend to focus on goal-oriented science, while industry tends to fixate on objective-oriented science. Success in academia is defined by advancing one's specific expertise in a particular research area for which the tangible measures of achievement include journal publications, research grants, and speaking engagements. This contrasts the productivity metrics — linked to the advancement of clinical candidates, IND (investigational new drug) filings, and product approvals — employed by industry research executives. These opposing reward systems must be acknowledged and addressed in order to achieve successful industry-academic collaborations. The creation of new intellectual property should be a primary shared incentive. Intellectual property is beneficial to both the industrial sponsor and to the academic institution and inventors. The value of intellectual property should be communicated to academics through the industry sponsor or the university technology transfer office. Productivity in the collaboration should be measured by visibility of the science, not volume of research. Industry managers should consider publications, presentations, and NIH grant applications as clear markers of progress. Finally, visible reinvestment in the collaboration can be considered its own reward and a clear sign of progress toward a singular goal. Thus, flexible reinvestment triggers should be established at the outset of the engagement by industrial managers in order to motivate both sides to achieve maximum productivity from the collaboration. L

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How Lab Improvements Can Drive Productivity

BILL MCMAHON

Bill McMahon is president, laboratory equipment at Thermo Fisher Scientific. He has been a senior leader with Thermo Fisher Scientific for the past six years. He has over 30 years of executive management experience working in industrial and consumer product sectors.

Today's laboratory managers are facing significant budget cuts while simultaneously being challenged to obtain faster results. These pressures have created an increased focus on identifying potential areas of lab productivity improvement. Lab managers are now more frequently looking for faster equipment, better storage capacity, and the ability of bench scientists to work on multiple instruments without having to stand in front of each one. When faced with these kinds of challenges, a complete process view of how the lab equipment is utilized, including staffing levels and space constraints, can be extremely beneficial.

IDENTIFY HIDDEN INEFFICIENCIES

Upon reviewing lab processes, it will likely come to light that bench scientists often face inefficiencies that they have adapted to and learned to work around. For example, the location of on/off switches or the height of handles can affect efficiencies; lab personnel have been observed retrieving a step stool or fashioning a homemade tool to reach a "hidden" switch. Examples such as these are often perceived as minor, but they are, in fact, extremely important to enhancing productivity. Lab managers and bench workers have, therefore, been working more closely with equipment manufacturers, allowing them to observe such daily practices. In doing so, the manufacturers better understand the scientists' pain points. Challenges can then be addressed through equipment that incorporates design elements such as a simple, one-touch lid opening for a centrifuge, or a highly visible green light indicating a correct temperature for an incubator. Features such as these will save valuable minutes to the scientist; this time adds up each day.

Space constraints within the lab also mean that location and size of equipment on the bench are considerations the lab manager needs to acknowledge when making purchasing decisions. Often, having a fresh set of eyes — perhaps from a different department or an outside partner or manufacturer — focused just on increasing productivity and implementing smarter working practices can prove valuable during this lab environment evaluation.

MAINTAINING SAFETY *AND* PRODUCTIVITY

Any lab manager will cite safety as their top priority, and rightly so. But safety should not be at the expense of productivity. As new equipment is developed based on the observed pain points within laboratories, then maintaining reliable uptimes will naturally be achieved while providing a safer working environment. For example, some new lab equipment has lids and latches that do not open while a machine is in use, providing a safe environment for both the samples and lab personnel. Add an indicator light when the equipment is off, and a scientist is both safe and efficient. And lighter-weight doors and shelves can reduce physical stress and injuries while also enabling faster movement of samples.

Consider the impact of rough corners or edges on equipment, or the repetitive operations performed by scientists. Identifying equipment that can circumvent these kinds of issues can result in safer and more efficient operations and less downtime from injuries or unnecessary inconveniences, such as getting a garment stuck on an edge. Also, instruments that can self-monitor or that incorporate service indicators can ensure that everything in the lab is maintained to operate at its safest and most efficient level. Some examples include triggers related to the number of spins in a centrifuge, freezer door openings, or hours of equipment usage. Utilizing equipment with remote monitoring capabilities is another way lab managers can maximize productivity. Such capabilities allow bench users to track sample progress and quickly identify instruments not currently in use, without being in front of the instrument itself.

The lab manager's goal should be to assess the entire lab workflow and identify areas that could benefit from equipment with, for example, smaller footprints and larger capacities to address space needs. Lighter-weight machines with more intuitive user interfaces will ensure easy movement and engagement. Remember, time, space, and utility are key drivers of productivity, and tomorrow's product R&D departments will constantly assess and refine these metrics.

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The Power Of Specificity

MARIO MOUSSA

They thought he had lost his mind. The business was teetering on the brink of bankruptcy, but the CEO had latched onto a decidedly nonstrategic topic: workplace safety. No one could possibly say it was unimportant, but concerned investors wanted to hear details about markets, revenues, and profit. Where was the business plan?

An analyst asked about finance metrics. Nothing doing. "I'm not certain you heard me," the CEO answered. "If you want to understand how Alcoa is doing, you need to look at our workplace safety figures."

You might recognize the speaker as Paul O'Neill, who merits a whole chapter in Charles Duhigg's *The Power of Habit: Why We Do What We Do in Life and Business*. A year after O'Neill gave his unexpected lecture about workplace safety to a group of dismayed shareholders and industry observers, company performance had rebounded and profits had reached record highs.

In bringing Alcoa back from the precipice, O'Neill pursued a strategy embraced by leaders in every industry: he got *specific*. He avoided the all-too-common CEO "cheerleading," as he put it dismissively, and focused on just one concrete thing. Research on positive behavioral change has confirmed the efficacy of pinpointing measurable actions and monitoring small, step-by-step improvements.

GETTING SPECIFIC REQUIRES BEING A STAR LEADER

My own research has shown that successful leaders use the power of specificity to create the conditions for peak performance. I like to say, be a "STAR." In other words, target Specific objectives, Take small steps toward achieving them, Alter the environment to remove barriers to action, and temper their aspirations with Realism.

To get specific with your own team, start by using "feedforward." Why feedforward? Traditional feedback is important, but it tends to be heavily focused on what went wrong in the past rather than what can be done differently in the future. Leadership coach Marshall Goldsmith coined this term to highlight the importance of looking ahead toward specific ways to make positive change. To see how this works, consider a colleague who always shows up late to meetings. Rather than saying: "You're always late, and it prevents us from getting to important items on our agenda," imagine saying something along the lines of: "If you aim to be at meetings 10 minutes early, it will help us make sure we can get started on time and hit every item on our agenda."

Getting specific is the key to inspiring passion and commitment on your team. Elite athletes achieve peak performance by focusing on small, realistic improvements that make a difference. So do great artists, brilliant scientists, and admired political leaders. They all behave like STARs. If you want to get the most out of your people, you should too.

Mario Moussa is the president of Moussa Consulting and the codirector of the Wharton Strategic Persuasion Workshop. He is the co-author of *The Art of Woo: Using Strategic Persuasion to Sell Your Ideas* and *Committed Teams: Three Steps to Inspiring Passion and Performance*, from which this column is adapted.

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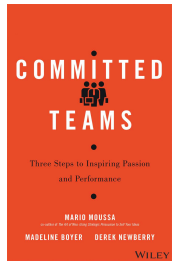

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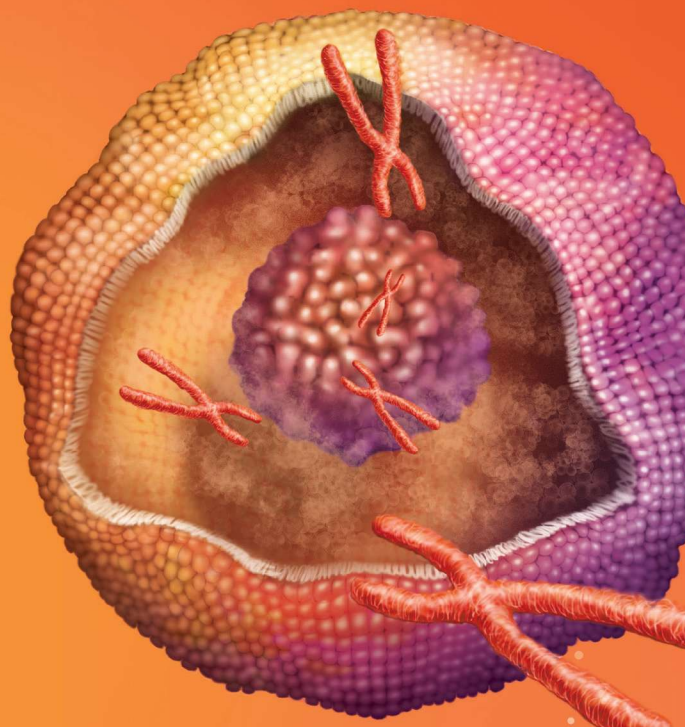

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