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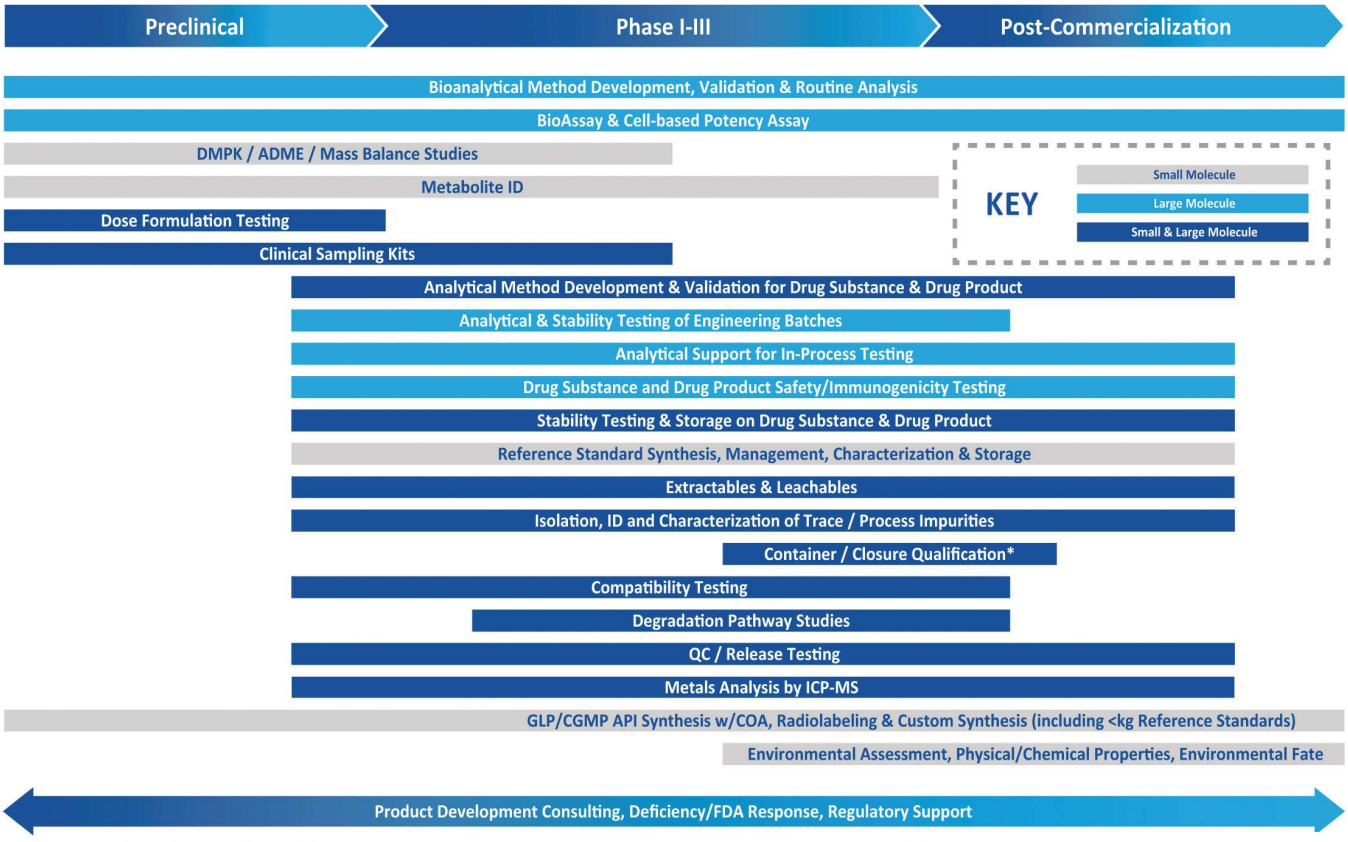


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# Why David Hale Is Considered An Icon Of Entrepreneurial Biotech

p. 36

> "If I were young again, if the idea were right, and the plan were right, I could still go out again and find an opportunity to start a company."
>
> David Hale
> CEO of Hale BioPharma Ventures, LLC

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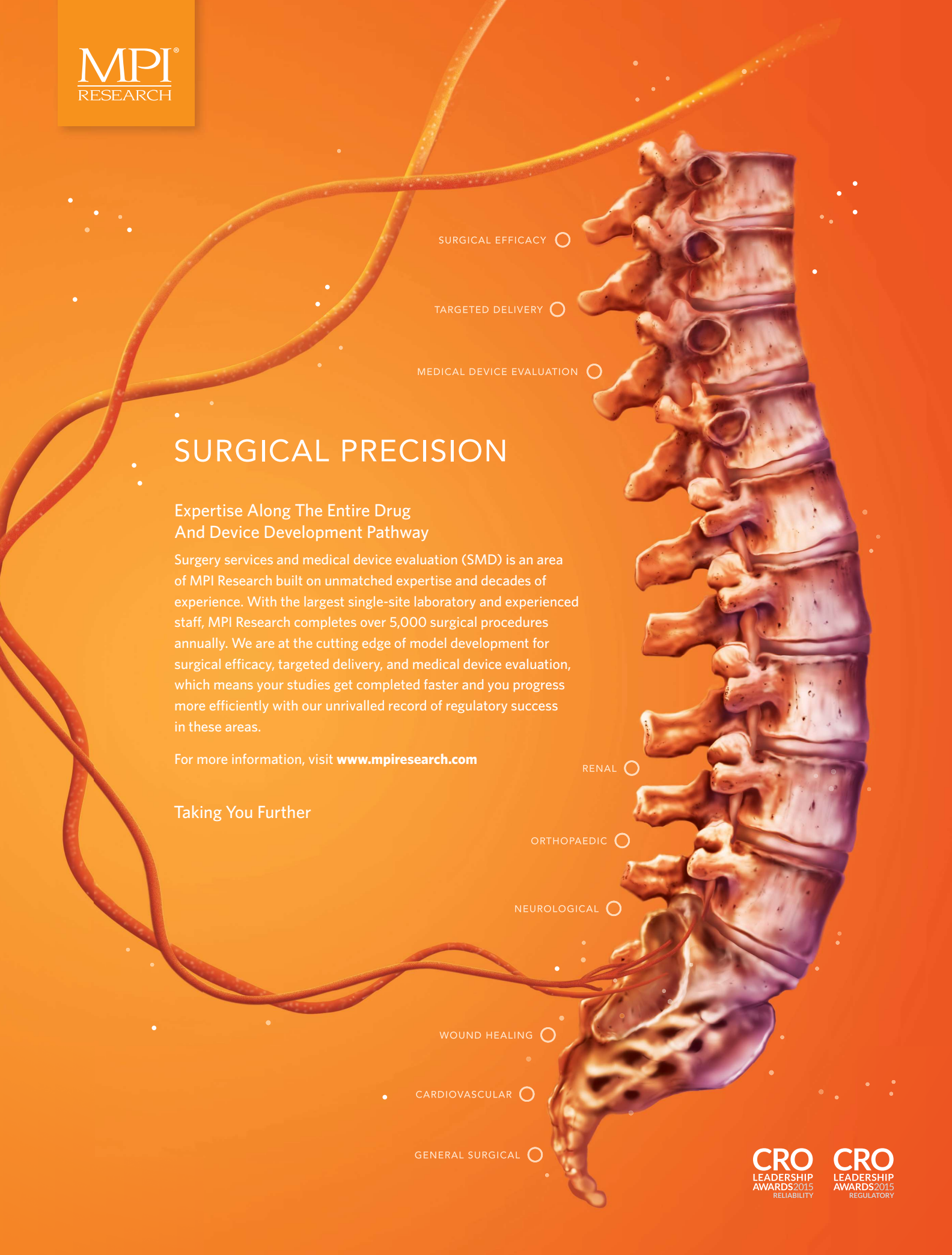


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# Are We Truly Investing To Meet The World's Unmet Medical Need?

**ROB WRIGHT** Chief Editor

A recent biopharmaceutical industry analysis by David Thomas and Chad Wessel (*Emerging Therapeutic Company Investment and Deal Trends,* June 2015) reveals that for the past decade oncology garners more investment than any other disease. How much more? In the United States for example, oncology collected 26 percent of every U.S. venture, IPO, and follow-on public offering (FOPO) dollar. Globally, 27 percent of all acquisition and licensing deals over the past 10 years involve oncology. This is analogous to placing 25 cents out of every healthcare investment dollar on finding cures for cancer, while divvying up the remaining 75 cents on the 100,000+ other diseases. Does this ratio make sense? If we were investing our therapeutic development dollars according to one of the drivers most often expressed by biopharmaceutical industry executives (i.e., meeting unmet medical need), would or should oncology still be number one?

According to WHO's most recent rankings of the world's deadliest diseases, the top five (annual mortality estimates in millions) are coronary artery disease (CAD) (7.4M); stroke (6.7M); COPD (3.1M); lower respiratory infections (3.1M); and trachea, bronchus, and lung cancers (1.6M). If this is the reality, why then does cardiovascular (CV), get about a nickel of every world disease's investment dollar? In fact, according to the BIO report, out of the past 10 years, 2014 was the absolute worst for CV in terms of both dollars and number of companies (only $52 million to 12 companies) for U.S. venture capital investment. Further, the report indicates that last year there were only three U.S. cardiovascular IPOs, four global CV licensing deals, and worldwide only one CV company acquisition. We know that 70 percent of our industry's clinical pipeline is attributed to small, emerging company development. And while entrepreneurship 101 would advocate that the reason most small companies are formed is to fill a gap not being met, if CAD is the scourge and unmet medical need that the WHO says it is, then why is there a total of only 129 clinical CV programs being conducted among our industry's innovation engine?

The CDC's 2015 most recent estimates seem to dispute the WHO, noting that of the 14 million people who will be diagnosed with cancer annually, 8 million will die. It is this number, along with the fact that the category of oncology comprises some 100 different subtypes of cancers (many of which with causes that remain truly unknown) that seems to justify oncology's definitive investment dominance. But does this really justify emerging company oncology clinical pipelines being tenfold greater (1,234 programs) than those for CV?

One of the biopharma buzzwords being used with increased frequency — "value" — often accompanies an industry spokesperson expressing the rationale behind their R&D programs as being driven by addressing an unmet medical need. I have heard executives express the desire to bring greater economic *value* to payers, add *value* to providers, and provide better *value* to patients. An April 2015 *Motley Fool* article suggests yet another value behind the cancer drugs that will be the biggest drivers of future pharmaceutical industry sales growth — profits. I don't have a problem with this. After all, who wouldn't be willing to pay for a cure for something like breast cancer? But the dominance of oncology investments makes you wonder if government and regulatory agencies need to reevaluate aligning drug development incentives with true unmet medical need. Though I understand the allure to invest in cancer cures, what "value" does that bring in a world where $3 out of every $4 spent on healthcare goes toward the treatment of chronic diseases (e.g., heart disease, diabetes), not oncology? L

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## Q What is the greatest insight gained from attending the 2015 ISPE/FDA quality week?

**A IN DISCUSSIONS WITH INDUSTRY AND FDA COLLEAGUES,** it is clear that understanding supply chain risks is the key to understanding risk of drug shortages. Over the past 10-15 years, the pharma industry has done an excellent job of reducing supply chain costs. However, we may have pushed our focus on efficient supply chains too far, contributing to the increase in quality issues and/or drug shortages in this same period. We recognize that, while we can learn much from supply chain structures in other industries like automotive or apparel, our risk tolerance in pharmaceuticals is different. New developments are changing our risk profile (e.g., shift from primary care to specialty care). Our burgeoning small and large molecule pipelines require agility that mature pipelines did not. The explosive growth in biologics demand will challenge our global capability to respond.

**ANDREW SKIBO**
is the head of global biologics operations and global engineering at MedImmune/AstraZeneca and the 2015 chair for ISPE's international board of directors.

## Q What is the key to a successful quality risk management approach in pharma?

**A DO NOT LOSE SIGHT OF THE BIG PICTURE.** This goes beyond putting in place a safety net and implementing risk tools at key processes. The question is, "How will an organization continue to assure quality control?" To succeed, the long-term vision and integration of a risk management platform must support the long-term goals and strategy of the corporation. This starts with having a forward-thinking mentality. As risk managers we often find ourselves focused on the details or identified risks. However, while these are critical to the overall function of the specific process, understanding the interactions and linkages of the "components" has the greatest impact to the organization in identifying areas for risk-control measures. Meanwhile, build flexibility into each component to allow room for evolvement. It is a delicate balance between thinking long term, while not losing sight of the day-to-day.

**JASON URBAN, PH.D.**
is director of global quality risk management and compliance at Celgene.

## Q How is the shift toward biologics and biosimilars changing the life sciences industry landscape, and what should executives be doing to capitalize?

**A MORE COMPANIES ARE ADOPTING THE "MODALITY-INDEPENDENT" APPROACH** (i.e., agnostic to whether the drug is a chemical or a biologic) to finding a therapeutic, which is a shift from the previous pharma versus biotech dichotomy. This is enabling technologies to cross over, and organizations are able to think broadly with more innovations. For example, a drug delivery technology typically applied only to a small molecule drug now can be married with a biologic or biosimilar, thus creating a new therapeutic that has a different profile and may have broader benefits. Biosimilars could be made into biobetters. As biologics mature, product differentiation will be the anchor for any new development program. Success now depends on how well these approaches are proactively strategized and executed so that both therapeutic and economic benefits can be achieved.

**SESHA NEERVANNAN, PH.D.**
is VP of pharmaceutical development at Allergan and oversees a wide variety of CMC (chemistry, manufacturing, and controls) activities related to drug development from early discovery to commercialization.

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# Thrasos Therapeutics

Using a novel mechanism in an obscure but nonsolitary space to prevent acute kidney injury and treat chronic kidney disease

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

## SNAPSHOT

Thrasos is developing two peptide drugs: THR-184, for prevention of acute kidney injury (AKI) in cardiac-surgery patients, and THR-575, for treatment of diabetic nephropathy, the leading cause of chronic kidney disease (CKD). Both drugs are intended to address apoptosis and inflammation and to slow the growth of scar tissue (fibrosis) in the twin organs by acting on the BMP/Smad (bone morphogenetic protein/Smad protein) pathway. Phase 2 trials of both candidates and lead indications are under way.

## WHAT'S AT STAKE

Some conditions are more common than we think. The big maimers and killers among diseases get all the attention. People constantly worry about cancer, heart problems, and infection, but they rarely think about their kidneys. Truth is, our kidneys often take damage we don't even notice, but which can affect almost every vital function in our bodies. One of the most frequent causes of acute kidney injury (AKI) is something we normally see as treatment — surgery.

As happens in life, we overlook some morbidities because we can't do anything about them. It's only when someone comes up with a solution that we take notice. I believe that is what will occur with kidney injury. The lead drug at Thrasos may awaken our awareness of this delicate and precious organ. It is not that the symptoms of AKI are invisible, but that their connections to the kidneys typically go unnoticed unless the organ damage is already known. Blood pressure, red blood cell production, and bone health are just a few of the functions tied to the kidneys. Surgery and other traumas can disrupt the complex protein chemistry that goes on in the twin organs. "When a nurse asks a patient just out of surgery if they need to pee, they are asking because they want to know if your kidney function is normal," says the company's CEO, Richard Andrews.

Thrasos is following a line of development stemming from the discovery of a pathway, BMP/Smad which has many functions, some directly linked to protection of the kidneys. "This pathway has the ability to protect the kidney from injury in ischemic and inflammatory environments, and it also has the ability to help temper the TGF (transforming growth factor) beta-induced fibro-genesis, the fibrotic process that causes destruction in long-term progression of injury to the kidney," Andrews says. The challenge was separating the kidney-related subpaths from the bone-growth tracks in the pathway. Thrasos identified some peptides that activate the specific proteins in the pathway that protect the kidneys but do not induce bone formation.

A competing, or possibly complementary, drug for AKI is under development at the Dutch company, AM Pharma, treating the condition primarily as an inflammatory state. This is a good sign for the company. Any so-called competition in a dormant space tends to increase awareness and market potential of that space.

Heart surgery is the most common surgical cause of AKI — thus, the clinical program for the lead Thrasos candidate is pursuing an indication for cardiac-surgery patients. AKI can also be triggered by many nonsurgical factors, from the seemingly benign, such as contrast-imaging agents, to mortal threats such as sepsis. But the result is the same: damage to kidney cells that prevent the organ from functioning normally. The therapeutic concept, protecting kidney cells, also may apply to CKD, which is the ultimate target of the second peptide-drug Thrasos is developing: diabetic nephropathy, the main cause of CKD. The current large Phase 2 trial in AKI, employing an adaptive design, should test the concept thoroughly.

**RICK ANDREWS**
CEO

### Vital Statistics

**22**
Employees

**Headquarters**
Montreal, Quebec

### Finances

Total raised about

**$80M**

in venture investment through four rounds. SROne, BDC led the D round; SROne led C round joined by ATV, Lumira, Fonds-FTQ, Pappas, SWCo., MP Healthcare Venture Management

### Latest Updates

**July 2015:**
Announced completion of 452-patient enrollment in Phase 2 clinical study of THR-184 for prevention of AKI in "at risk" patients undergoing cardiac surgery. Data is expected in January 2016.

**March 2015:**
Completed a $21M Series D financing

**September 2014:**
Announced completion of interim analysis of Phase 2 trial of THR-184: study will continue with high dose after data review.

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# Rx Industry Fighting Off New Salvos To Extract Medicare Savings

**JOHN McMANUS** The McManus Group

When the *King v. Burwell* verdict upholding the Obamacare subsidies was announced, Republicans in Congress breathed a collective sigh of relief. Yes, most of them thought the law was unconstitutional, and a clear reading of the statute that subsidies could only flow to an exchange "established by a State" caused flummoxed consternation. But they had dodged the bullet of what to do with the 7 million individuals receiving subsidies through the federal exchange who were about to lose their coverage.

The Republican conference was split between those who continued to want full repeal of Obamacare and those who believed currently insured individuals needed at least some transitional relief, as Democrats had already teed up compelling case studies of cancer patients halfway through chemotherapy regimens and other such sob stories. The Republican conference was in a no-win dilemma of either inflaming their base or walking into the punch of potentially disrupting care of real-life patients.

But the disposition of that case and the full repeal of the dysfunctional Medicare physician sustainable growth rate (SGR) payment formula earlier this year have fundamentally changed the healthcare legislative paradigm in Congress. No longer are all legislative efforts focused on the annual "Doc Fix" bill with healthcare interests attempting to insert or exclude various provisions in that omnibus package.

Rather, we have entered a more free-wheeling environment, which has freed committees of jurisdiction to move more modest stand-alone bills, in which supporters have to demonstrate support the old-fashioned way – building bipartisan cosponsors and stakeholder support for discrete issues and legislative solutions. Nearly all of the bills have substantial bipartisan support. The Ways and Means Committee recently marked up 10 bills, six of which have been approved by the House. The Senate Finance Committee marked up 12 bills, all of which received voice votes and are ready for floor action.

The Energy and Commerce Committee culminated its yearlong effort on a "21st Century Cures" package of modest reforms to the FDA approval process for drugs and devices and an infusion of nearly $9 billion of resources to the National Institutes of Health with a strong bipartisan vote of 344-77 on July 10. The committee had abandoned more aggressive reforms to promote innovation through new patent extension and other exclusivity enhancement proposals.

But the pharmaceutical industry soon learned it could not get caught flat-footed by these deceptively innocuous packages. Many of these proposals suggested "pay-fors" — or resources — from the life sciences industry to help finance desired goals. Less than two weeks before 21st Century Cures was sent to the floor, the Energy and Commerce Committee floated a policy to change Medicare Part B reimbursement of biosimilar drugs from average sales price (ASP) + 6 percent to ASP + 8 percent. Such a policy would reward physicians with higher reimbursements for prescribing the biosimilar product rather than the brand-name product, and the Congressional Budget Office determined that it could result in savings of more than $1.3 billion over 10 years, betting that physicians would be encouraged to switch to less costly products.

The Energy and Commerce Committee also considered hiking brand-name copays for "low income subsidy" Medicare beneficiaries to encourage greater utilization of generics. The thinking was apparently that the current 80 percent generic fill rate for those beneficiaries was not high enough.

Though the pharmaceutical industry was able to beat back those proposals, several other industry pay-fors made it into the House-passed 21st Century Cures bill. The bill would exclude authorized generic drugs from average manufacturer price (AMP) calculations, thereby increasing

*"It might be hard for industry to justify why physicians should be paid more for administering a drug simply because it costs more, particularly when the sky has not fallen when sequestration already reduced the 6 percent add-on to about 4 percent."*

the AMP of brand-name drugs and the corresponding Medicaid rebates manufacturers pay the state governments.

In addition, the Cures bill also includes a pharmaceutical payment cut that first popped up in one of the innocuous bills Ways and Means reported earlier this spring to establish a value-based insurance design demonstration program in Medicare Advantage. The provision cut reimbursement for durable medical equipment-infused drugs, which were still paid at 2003 rates of average wholesale price. You know a policy is going to eventually make it over the finish line and become law when it shows up in multiple packages to finance totally unrelated items. (They can keep recycling it, until it actually becomes law.)

The industry is now confronting new recommendations by the Medicare Payment Advisory Commission (MedPAC) June Report to Congress, which questioned whether the 6 percent add-on payment for Medicare Part B drugs creates incentives to use higher-cost drugs. MedPAC suggests abandoning the percentage add-on and just providing a flat fee, regardless of the underlying price of the drug. It might be hard for industry to justify why physicians should be paid more for administering a drug simply because it costs more, particularly when the sky has not fallen when sequestration already reduced the 6 percent add-on to about 4 percent.

The larger point is that the industry cannot be sanguine that the nuclear bomb of price controls for Medicare Part D (saving upwards of $130 billion) is off the table because Congress has repealed the SGR (sustainable growth rate) physicians' cuts; other more-targeted hits are being lobbed at the industry. More conventional warfare is now the norm, and the industry must scramble to put out sprouting brushfires.

## PATENT BILL VOTE DELAYED AS OPPOSITION MOUNTS

Meanwhile, lobbying intensity on Judiciary Chairman Goodlatte's high-tech-friendly "Innovation Act" patent reform bill has escalated, and the life sciences industry has finally begun to get traction. The bill barreled out of committee with only a few dissenting votes, and Goodlatte refused to make any substantial concessions to biopharma's request of reform for the new *inter partes review* (IPR) process at the patent and trademark office. Certain hedge funds had exploited that process to either short targeted companies' stocks or extract settlements. But high-tech companies had utilized the process to effectively knock out "nuisance" patents from so-called patent trolls — shell companies with no real product at stake.

In a July 15 letter to the bicameral Judiciary Committees, BIO and PhRMA requested an exemption from IPR for products approved by the FDA, noting that the patent resolution framework under Hatch-Waxman and the Biologics Competition and Innovation Act provided the industry with unique treatment that both "1) increase the ability of generic and biosimilar manufacturers to offer consumers lower-cost versions of off-patent medicines, and 2) preserve incentives for the discovery of new, innovative medicines."

The biopharma industry locked arms with venture capital and a host of patient groups that were counting on innovation to address unmet medical needs and mounted a lobbying blitz, arguing that IPR brought a high degree of uncertainty to the development of costly new therapies. But they were countered by insurance plans and the AARP, who argued that "an IPR exemption would result in 'evergreening' where manufacturers make minor modifications to existing products in order to extend patent protection for years." AARP asserted that the carve-out could result in billions of more spending by Medicare and Medicaid on drugs whose patents were not legitimate.

But the biopharma industry contended that the Hatch-Waxman patent regime, which is unique to the industry, is working to promote competition — with 88 percent of prescriptions being generic as solid proof.

While Goodlatte and the leadership have not yet agreed to the IPR exemption, the scheduled House vote in July has been delayed to September at the earliest. That is welcome news, but also gives both sides time to mobilize during the August Congressional recess. L

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

# Warning: Don't Let Bio-Euphoria Distract You From Being Disciplined

ALLAN L. SHAW

*"Innovation should go well beyond the science and apply to all aspects of an organization's operations."*

It has been a record-breaking period for the industry in almost every category, characterized by robust performance, exciting growth prospects, and hope for the patient community. In the backdrop, the shift in Big Pharma's resource allocation has fueled hundreds of billions of transactions, driven by its desire to improve operational and capital efficiency, reflecting:

- increased emphasis on external collaborations and a de-emphasis on internal research, as illustrated by the dramatic downsizing of Big Pharma research centers such as Roche's Nutley facility and the increasing presence of Big Pharma in research centers aligned with universities, such as in Kendall Square and the Upper East Side of New York City.
- changing focus on depth (e.g., what a company is especially good at) as opposed to breadth (e.g., "jack of all trades, master of none") as illustrated by the GSK-Novartis business exchange of their respective oncology and vaccine portfolios.

Essentially, this shift recognizes that smaller, more nimble biopharma companies are more efficient in the research and development of innovative medicines. Collaboration is also key to this shift; alliances play an important role in enabling capital/time-efficient development that leverages core technologies/competencies while allowing for the prospect of developmental synergies. And finally, scale (e.g., the wherewithal to enable and facilitate more studies, indications, combinations, and head-to-head comparisons) will be a key success factor to achieving an advantage in less-differentiated markets, particularly from clinical, regulatory, and patient-access/payer perspectives.

In such a "land-grab environment" where everyone is a target and capital access is easy, there is an inherent risk that complacency will set in. This is particularly problematic, as it is always important to remain strategically and operationally focused and financially disciplined, especially in an environment where performance is not the only factor that could attract the attention of activist investors (e.g., Allergan vs. Pershing Square/Valeant). Given the increased scrutiny on resource allocation as a driver of value, I would like to offer some suggestions concerning several high-impact focus areas that require continual assessment and recalibration:

- Portfolio management: optimization and prioritization are critical as portfolio activities fundamentally transcend capital allocation decisions across an organization.
  - Differentiation is critical for success in a changing commercial landscape. This necessitates emphasis on innovative targets for unmet patient needs. At the top of the consideration hierarchy for all developmental candidates are fundamental questions, such as "What is its comparative effectiveness to the standard of care?" and "Is there a strategy for developing the value proposition for new drugs?" Given the correlation to long-term value creation, it is imperative to assess a product's commercial viability and ensure the target product profile (TPP) is compatible with these objectives.
    - As part of the portfolio assessment, it is important to consider potential indications and regulatory pathways, views of KOLs and patient advocacy groups, and the methods that managed care will employ to evaluate and reimburse for the product. These activities provide decision support. They facilitate a better understanding of the value proposition and/or identify issues and potential pitfalls (before significant investments are made).
  - We must remain mindful of the very fluid competitive landscape, particularly with respect to

development efforts. There is an increasing prevalence and clustering of innovative activities concentrated on common targets, reflecting capital inefficiency. This dynamic is best illustrated by the recent ASCO 2015 conference that highlighted the industry's focused developmental efforts on a limited number of cancer targets. This "lemming mentality" will inevitably create self-inflicted wounds as the innovative premium is cannibalized by alternative products that may even be perceived as inferior. Solvaldi and Viekira Pak are classic examples, highlighting the pharmacy benefit managers' (PBMs) emerging purchasing power and emphasis on minimizing current-period costs over healthcare system costs. This underscores the need to better correlate resource allocation to market forces (e.g., competitive landscape and patient needs) to better inform and optimize drug development activities. Otherwise, we are sowing the seeds to accelerate the commercial marginalization of truly innovative science.

- Addition by subtraction: capital-efficient organizations "kill" programs early and establish pipeline decision mile markers along with ROI metrics. There are too many instances of developmental programs being maintained as well as rationalized for the wrong reasons (e.g., emotional attachment, cajoling to the investment community). Unfortunately, this does not change reality or the underlying fundamentals and will only result in value destruction and lost credibility.

- Cost structure can be a lightning rod for self-inflicted wounds, and it needs to be proactively challenged.
  - Innovation should go well beyond the science and apply to all aspects of an organization's operations. Besides the obvious need to continually benchmark operational performance against your peer group to identify areas for improvement, there are inevitably other cost-effective ways to achieve business objectives. Simply put, it is about working smarter, not harder, and overcoming institutional bias to effectuate change. This is obviously much easier said than done and best exemplified by a riddle I often tell my staff (in my life as a CFO) before embarking on a project: "Why did the auditor cross the road? Because he did it last year." In a fast-moving, evolving environment, it is important to challenge the status quo and encourage out-of-the-box thinking.
  - In my opinion, commercial operations provide an area of low-hanging fruit that could benefit from resource optimization, particularly in an environment where detailing is going the way of the dinosaur, as physicians become less responsive to expensive field sales forces and a regulated marketing environment. Recognizing and embracing this paradigm shift will yield cost-effective solutions to engage stakeholders, such as innovative marketing programs including digitization strategies (e.g. edugaming) to reach physicians and patients.

- The balance sheet is a strategic tool, not a scorecard. Continue to improve capital allocation and leverage the ecosystem to stretch capital and unlock value.
  - Retain discipline with capital deployment. Organizations are generally more effective with capital deployment when they have less as opposed to more. Do not fall into this trap; it is critical to remain strategic and smart about resource allocation because your "pot" may not be as large in the future. It is foolhardy to take things for granted, such as easy capital access, and assume the party will continue.
  - Maintain alignment of operating activities with strategic objectives:
    - Stay focused and committed to your core expertise, and understand your differentiation.
    - Leverage the vast capabilities of the ecosystem, and avoid recreating the wheel. Remember, the shortest distance between two points is a shortcut — collaborate, collaborate, and collaborate whenever possible.
  - For public entities, consider utilizing your stock or "second currency," particularly at prevailing valuations, to build upon your capabilities and mitigate risk.

The bottom line is that it is important to run your business unbridled by the industry hubris. At the same time, remember it is impossible to determine — much less control — how long the capital market spigot will remain open or if the parade of M&A transactions will continue at its frenetic pace. While there are no guarantees, particularly given inherent industry risks, capital-efficient organizations and stakeholders (including patients) will be rewarded for cost-effective development/accelerated time to market. Remember how you got here, and do not lose your focus or discipline during this period of "bio-euphoria." Stay true to your principles, and do not succumb to temptation; there are already too many people drinking from the punch bowl. The optimal deployment of organizational resources will inevitably become an increasingly important metric in differentiating management's performance when the music stops. L

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HOW BAYER RELIEVED MY INNOVATION NEUROSIS | By L. Garguilo

# How Bayer Relieved My Innovation Neurosis

**LOUIS GARGUILO** Executive Editor @Louis_Garguilo

*Among her many positive attributes, Dr. Monika Lessl is a good sport. I know because she graciously accepted to enter – at least for the duration of our interview – my neurosis regarding the word "innovation."*

This ailment intensified at BIO 2015 in Philadelphia, where Lessl and I sat down to talk. Others devoting a career to innovation — and holding a title like VP, Head of Innovation Strategy at a renowned company like Bayer AG — would walk away from a conversation that starts with: "Innovation is meaningless in the bio and pharma industries. The word itself drives me crazy." Lessl didn't leave, though. Instead, by meticulously imbuing the word with context and revealing the meaningful way Bayer has woven innovation into the entire company, she walked me through my difficulties with the word. Here's how our session unfolded.

## We Breathe … Air!

This issue with innovation started a few years ago, rising to a jarring crescendo at the BIO International Convention, where at virtually every other step, every presentation, booth, and marketing material, and in each conversation, someone or some company was better or more worthwhile for having appended innovation to their activities. Nary a soul performs boring R&D; all innovate technology, platforms, and programs. Passé corporate

**MONIKA LESSL, PH.D.**
VP, Head of Innovation Strategy at Bayer AG

> "Innovative leadership is different than leadership. The first is both a product of a purposely created environment and the cause to make ideas happen."

culture is replaced by an innovative environment. Worn-out relationships must become innovative partnerships. There is no more naked planning; it is all about innovative strategies. Please … make them stop.

In my despair, I ask Lessl if this incessant invocation of innovation doesn't start to wither on the vine of meaning. Hasn't it become as innocuous as saying, "We don't just breathe … we breathe air!"?

"Yes, there is this added challenge to be meaningful because everybody is now talking about innovation," she replies. "The key is in the actual doing. Innovation is defined by the actions we take." Lessl says Bayer has constructed a model for action that both enables and defines innovation for its employees and external collaborators. But before we go there, I lament how years ago there was "creation," a term of biblical — and great scientific — proportion: From nothing comes something. Now that's exciting. Today, though, we want "innovation" to mean more than just some alteration of that which already exists. "On the first day, he or she … innovated?" When did innovation crush creation and relegate it to second fiddle in the biotechnology and pharmaceutical industries? Why isn't Lessl titled Head of Creation?

We laugh at my insanity. Then Lessl says more seriously, "Creation — creativity — is of course still absolutely crucial. But there is a real point here. We've learned creation is not enough. Create, and then turn that into a product that serves patients, customers, and farmers for agriculture. People do mix the two up and say that innovation is simply an ideation process. It is not true. The idea is critical, but the translation to bring it forward is where we can often fail. And it requires passion, and persistently great leadership, to get the initial idea to a product of value and out to the market. So, for example, innovative leadership is different than leadership. The first is both a product of a purposely created environment and the cause to make ideas happen."

## There's A Creation For That

Is creation, then, a done deal? Has the industry mastered the art of coming up with original ideas and novel approaches, and so now the focus must be on the culture to move them forward? People used to care more for the epiphanies; now it's all about the environment within which they are born.

Lessl, who joined Bayer HealthCare in 2007 and has had the word innovation in her title from that start and in each successive promotion — the first role was Director, Alliance Management Global Innovation Sourcing — is not new to this type of discourse. Much of what has developed around the idea of innovation at Bayer stems from her earlier experiences there and even before she joined the company, including when she served as CEO of the Ernst Schering Foundation. She originally joined Schering AG in 1994 and moved to Bayer when Schering was acquired in 2007. She has published articles with titles such as: *Interactive Added Value: New Innovation Models Between Industry and Science* and *Collaborative Innovation — Regaining the Edge in Drug Discovery*.

Regarding the question leading this section (i.e., Have we mastered the art of coming up with new ideas?) and the current focus on innovation, Lessl sees the process of collaborative thinking as the connecting thread. "If you want to be successful, you have to do both the creation and the translation, right?" she asks. "Fundamental to the creation part is thinking. Creativity is a form of thinking that is then enhanced and actually continued within an innovative culture. At Bayer, we focus on integration as a cross-functional approach to collaborative thinking. Different perspectives, opinions, and expertise help us come up with new ideas, new ways to move those ideas to development, and ultimately a commercial product."

Lessl interjects that Bayer has been a successful company for more than 150 years, but "we have to constantly work on developing new processes and capabilities to stay successful. This is what we are doing and what we continue to explore throughout the organization, including our 4 Cs Model of Innovation."

## The 4 Cs Of Innovation

Lessl explains this as a holistic model for people and their ideas. The model assists with the creation, nurturing, and enhancing of people and ideas. Its goal is to create superior employees, products, and services. Here's a summary.

1. ***Cultivate***
   This refers to finding and establishing the right environment so people can "think out of the box," and the right ideas can grow. It also refers to supporting people with the right skills, tools, and leadership mindset.

2. ***Connect***
   People need to reach out to various partners to obtain additional expertise and inspiration to further develop ideas. To support this, Bayer "continuously works to develop

novel and innovative ways of partnering."

### 3 Collaborate

To "make ideas happen," you need to then join forces both internally and externally. For example, Bayer has established an internal platform called *WeSolve* for collaborative problem-solving.

### 4 Communicate

Companies need to effectively communicate to attract talent, partners, and customers to assist in creating and progressing novel business offerings.

If Lessl had to pick one of the four as the lynchpin of innovation, it would be the fourth, communication. She makes it clear, though, that all are crucial and must be applied equally internally and to all external partners. "We've put a lot of thought into how we can promote innovation in our organization. On the one hand, as we've discussed, a lot of it does clearly refer to and inform R&D strategies, which define in what areas we want to innovate. But innovation up to and through the marketing and sales of commercial products leads to the correct mindset and spirit for the whole organization and all partners."

Based on these guideposts, Lessl says Bayer has "developed a whole range of collaboration models and experimentation." She mentions very close research relationships with the Broad Institute here in the U.S. and the German Cancer Research Center — which, she points out, has nearly 3,000 people working on cancer, the most in Europe — to broader open-innovation platforms, crowdsourcing (see more on this in the accompanying article), and venture funding.

## Is Bayer Known For Innovation?

Innovation has been of top importance at Bayer for a long time, says Lessl, and much of the recent activity is based on acquired learning and experimentation. "You can see this in the fact that we have a board member, Kemal Malik, directly responsible for innovation at Bayer," she says. *Life Science Leader* featured Malik in our April issue, where he simplified innovation as "turning a new idea into something meaningful for customers." (He also said, "When you ask people what innovation means to them or even just what innovation is, they get

# Bayer's Trust In Crowdsourcing

**Be honest:** When was the first time you heard of and/or started to think about crowdsourcing (if ever)? Or more specifically, crowdsourcing applied to the biotechnology or pharmaceutical industries? If you're like me (and there is a measure of pity if so), it wasn't that long ago … and any thoughts on the subject were more about crowd*funding* (gaining investments or donations from strangers) than anything else.

That's not the case for Monika Lessl, Ph.D., VP, head of innovation strategy at Bayer AG. She jumped into the "crowd" in the early 2000s, while CEO at the Ernst Schering Foundation in Berlin, and started utilizing crowdsourcing in 2009 at Bayer HealthCare. In her article, "Crowdsourcing in Drug Discovery," published in *Nature Reviews* in April 2011, she penned, "Crowdsourcing is emerging as an open-innovation approach to promote collaboration and harness the complementary expertise of academic and industrial partners in the early stages of drug discovery." Prescient, you might say.

How did Dr. Lessl latch on to crowdsourcing so quickly?

"It seemed so compelling to me," she says. "You simply cannot meet all the challenges of being a pharmaceutical company alone. Every company should understand that more than 99 percent of research done is outside your own walls. Why not ask people for their ideas?"

## On The Cusp Of The Crowd

Under the tutelage of Dr. Lessl, Bayer HealthCare started its crowdsourcing activities with the *Grants4Targets* program, which provides grants for the exploration of attractive, novel drug targets and biomarkers in the fields of oncology, gynecology, cardiology, hematology, and ophthalmology. "We had some contentious discussions on should we try this or not," she says. "I mean, in the beginning, the discussion wasn't even about will we get *good* ideas; it was, 'Will we set this all up and get nothing at all?' Others said we would just get a lot of crap!"

Lessl, though, saw the program as a legitimate business experiment to understand if crowdsourcing was an avenue to more and improved early-stage ideas. It didn't take long for Bayer to decide it was a road well taken. "It was successful," explains Dr. Lessl, "and I think that's because of the way we set up the whole scheme."

Dr. Lessl says the first key component was easy access; anybody with Internet access could participate. Next it had to be an unbureaucratic process, with bureaucracy the antithesis of the crowdsourcing movement. The final point, though, required the most internal debate: Bayer would not own any of the IP at this stage. Both parties would have to subsequently and mutually decide they wanted to move forward into a collaboration agreement. This debate was won, and she says this is indeed the most significant point to understand about crowdsourcing: Where there is no trust, the crowd disperses.

## Trust In The Crowd

Dr. Lessl learned during her five years at the Ernst Schering Foundation that trust is the glue that keeps the crowd together. "You don't get far without trust," she says. "If the people trust you, they are happy to work with you. For example, if you support fellows in a foundation, it's considered a donation; you don't have a right to get anything back. However, have you ever noticed how people are bound to foundations because they feel trust in the relationship? It was my job to translate this understanding to Bayer."

Today, applicants receiving grants from *Grants4Targets* are only obligated to provide a research report. "Thereafter," says Dr. Lessl, "in principle they can take their money and their results to another company. It is important they feel that freedom." However, she adds, few if any take up that option. "We build a relationship that keeps them. For example, we nominate a coach for each grant — an internal champion — to support the development on all fronts. So, via that trust and the relationship, new creativity and ideas are reaching Bayer." She concludes, "Many collaborations fail not because of business terms, but because of a poor relationship."

## Going Viral

Back at Bayer, Dr. Lessl says after the first crowdsourcing experience, "It really went viral." Other R&D departments adapted the concept, and *Grants4Leads* was born to address the next step in the drug discovery process. Even Bayer's IT departments wanted in on the concept. "They said, 'Well, why don't we make a grant for apps,'" recalls Dr. Lessl, and started to work with start-ups developing healthcare applications that complement Bayer products. One example from Bayer's *Grants4Apps* program is an app linked to a small pillbox that sends a positive message to patients' smartphones if they take the pill as prescribed, and a different message — "Take your medication" — if they don't.

Bayer now has four distinct Web-based crowdsourcing initiatives, with the fourth called *PartnerYourAntibodies*. "We are just on our way to bringing it all together for both our healthcare and crop sciences fields," she says. "Already, though, I think we are ahead of the curve in the pharmaceutical industry in establishing crowdsourcing as a part of our overall innovation theory." Last year, as a result of a crowdsourcing activity, Bayer announced a collaboration with the University of Oxford in the U.K. "Crowdsourcing can bring many short-term relationships through a seed approach, but it also can result in long-term research alliances like with the University of Oxford," she says. "The potential for both is great."

a confused look on their faces. They have a tough time explaining it." Thank goodness it isn't just me with the problem.)

Ultimately in business, though, dollars denote commitment. Lessl says a demonstration of Bayer's commitment to innovation is an increase of 10 percent in the R&D budget this fiscal year. She also points to last year's $14 billion acquisition of the consumer-care business of Merck & Co., Inc., which included $7 billion of notes in Bayer's largest dollar-denominated bond issue that helped fund the purchase. According to Bloomberg, it was the seventh-biggest dollar-denominated corporate bond sale of 2014, and Lessl says Bayer won a corporate finance award in Germany for this innovative transaction.

However, even with these growing, widespread, and impressive activities of innovation, I wonder if Bayer still isn't more known for other attributes. "Maybe Bayer has been seen more as being efficient, stable, reliable, professional, and not for being agile," says Lessl. "But that perception of reliability and stability is a clear strength, and we'd like to keep it. We also want to be recognized for the actions we have taken on the front of innovation." After a pause: "Do I have to explain what innovation means again?"

No, Lessl, you don't. I've got it, and so does Bayer. In the end, innovation is itself a form of creation. It is the creation of an environment for people and ideas to flourish. Perhaps in some regards it is nothing more than the cold calculation of simple addition and subtraction. Add the components, people, and even companies that assist in translating better ideas into better services and products for patients and customers, and provide better returns on investments and to investors. Subtract any items wherever they are in the company if they hinder the process of collaborative thinking to make it happen. And so, innovation itself becomes the business strategy today in the biotechnology, pharmaceutical, and for Bayer, agricultural markets. Will it work? We'll continue to see. And if you have the time, please check out my recent article on Outsourced Pharma titled, *Can Bayer Innovate the Incubator for Japan?* Looks like I've made a full recovery.

# CAN NANO BRING US BACK FROM PERSONALIZED TO MASS MEDICINE?

By L. Garguilo

LAURENT LEVY
CEO of Nanobiotix

# CAN NANO BRING US BACK FROM PERSONALIZED TO MASS MEDICINE?

LOUIS GARGUILO @Louis_Garguilo

How big can a singular change in perspective be? As big as a Copernican Revolution, you might say. Or more precisely, perhaps, how small can it be? If it's the fundamental change that creates a meta-theory moving biology to physics, it can be as small as building particles — or deconstructing them — atom-by-atom to bring new drugs to mankind. This is the big and small of nanomedicine (nano).

With the arrival of nano, there are now three pillars of medicine steadying the hopes of patients: bio, pharma, and now *nano*. But don't make the same mistake many people in pharma made during the advent of bio; nanomedicine is no pie-in-the-sky concept — it *has* arrived. "We can count 40 nanomedicine products on the commercial market," says Laurent Levy, CEO of the Paris-based, oncology-focused nanomedicine company, Nanobiotix. "At least some 200 more are in clinical development."

While scientific revolutions move thought in different directions, rarely is that direction backwards. With nanotechnology applied to drug development, though, we might end up further away from the need for precision medicines and return to the promise of mass production of drugs, including oncologics.

Whichever the ultimate direction, no discussion within the realms of drug discovery, development, and manufacturing — not immunotherapy or ADCs (antibody drug conjugates) — holds more potential scientifically, and perhaps revenue-wise, than that of nanomedicine. Says Levy: "Nano is the story. Now is the time to make sure all people understand."

## UP TO HERE-AND-NOW IN NANOMEDICINE

The first FDA-approved nanodrug was Doxcil (Sequus Pharmaceuticals) in 1995. According to the *Journal of Controlled Release*, the drug is important for at least these two reasons: prolonged drug-circulation time due to the use of nanoliposomes and drug release at the tumor.

"That's the first approach of nano: Make an existing drug work better utilizing a nano-sized delivery system. Nanomedicine started in formulation development," says Levy. By encapsulating a drug in a nano-liposome — purposely designed and smaller than ever before — you can change the distribution of the product in the body, hide the molecule, reduce toxicity, and increase efficiency in targeting tumors. If this sounds a lot like the minirevolution of antibody drug conjugates, Levy says nano can help overcome current limitations of ADCs ... and offer alternatives.

As exciting as these applications of nano are, Levy, in a soft, conspiratorial voice, says the focus has expanded dramatically. "There is a new game in nano. We don't need the drug anymore. The nanoparticle is the active principle."

Heady stuff; but before going there let's stay focused a bit more on where we are currently. To help understand the status quo, Levy references an article in the publication *Nanomedicine*, "The big picture on nanomedicine: the state of investigational and approved nanomedicine products."

As if channeling our needs, it begins: "Developments in nanomedicine are expected to provide solutions to many of modern medicine's unsolved problems, so it is no surprise that the literature contains many articles discussing the subject. However, existing reviews tend to ... take a very forward-looking stance and fail to provide a complete perspective on the current landscape."

For many of us, nanomedicine surfaced in 2005 when Abraxis BioScience's Abraxane became the first nanodrug for breast cancer sanctioned by the FDA for the treatment of metastatic disease. Celgene's 2010 buyout of Abraxis put an emphasis on the nano industry. The clinical and financial opportunities for nano were amplified with the FDA's subsequent approval of the drug for the treatment of nonsmall cell lung cancer and for patients with advanced pancreatic cancer — one of the most difficult treatment areas in all medicine.

Detlev Biniszkiewicz was an early adopter of nano when he was VP of Oncology-Strategy, External Science & Licensing at AstraZeneca. In late 2013 he said, "The deal I am really excited about is the one we did with CytImmune [a clinical-stage nanomedicine company focused on multifunctional, tumor-targeted therapies]. Here we really want to push the envelope by loading one nanoparticle on two different drugs that have been shown to have synergistic effects in a preclinical model." He added, "We would have had to develop two different drugs, and after years and years, hope to combine them. Instead, we are looking for nanotechnology to develop a truly disruptive innovation."

Interestingly, while this example pulls the future directly into the present, it also introduces an old challenge for pharma — the loss of talent to burgeoning industries such as bio, and now, nano. For example, in April Biniszkiewicz decided to take what he learned at AZ to Surface Oncology Inc., a company focusing on immunotherapies, where he is now president and CEO. Indeed, according to the latest numbers published by the European Technology Platform for Nanomedicine (ETPN), there are already 400 start-ups devoted directly to nano in Europe, and as many as 200 in the U.S. Competition for nano-talent can only continue to increase.

Back to the *Nanomedicine* report, it goes on to list hundreds of nano-related products commercialized or in the clinic. It also points out the difficulty in locating information on nanomedicine products. This has been partly due to the lack of a clear definition and categorization of nanomedicine as a unique product class. To solve this, the National Cancer Institute (NCI) and FDA have led efforts to standardize characterization of nanomaterials and the collection of information on nanomedicine products. NCI established the Nanotechnology Characterization Lab (NCL), which developed a "standardized analytical cascade that tests the preclinical toxicology, pharmacology, and efficacy of nanoparticles and devices." Already,

> *"It is not about personalized medicine anymore, but mass medicine."*

NCL has characterized over 200 nanomaterials from academia, government, and industry. And it now has a complement: The European Nanomedicine Characterization Laboratory (EU-NCL) was established in June, as a partnership of analytical facilities in France, Italy, Germany, Ireland, the U.K., Switzerland, and Norway.

Much earlier, the FDA Office of Pharmaceuticals Science (OPS) released a Manual of Policies and Procedures (MAPP 5015.9) instructing reviewers on gathering information on nanomaterial size, functionality, and other characteristics for use in a database. This manual provides a more inclusive definition of "nanoscale" and "nanomedicine" that encompasses any material with at least one dimension smaller than 1,000 nm. Why does size matter here? Most importantly because an object this small is uniquely capable of achieving properties and cellular effects not achievable without this nanoscale.

Marketwise, estimates vary because of this difficulty in categorization, but according to one analysis (BCC Research, "Nanotechnology in Medical Applications: The Global Market), the global nanomedicine sector was worth $53 billion in 2009, and it was projected to surpass $100 billion in 2014.

Levy himself seems involved in all parts of the discussion above. Nanobiotix's first product — NBTXR3 — is nanoparticles designed for direct injection into a cancer tumor to direct and amplify the effects of radiation in the tumor and direct radiation away from surrounding tissue. NBTXR3 is currently in Phase 3 (scheduled to conclude in 2016) for patients with soft tissue sarcoma. Directly behind that indication are trials

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for liver and head-and-neck, rectum, and prostate cancers. A study commissioned by Nanobiotix estimates the market for this nanoparticle technology (NBTRX) at $5 billion to $6 billion annually.

Levy also plays a major role in the ETPN, acting as its vice-chairman. The ETPN is taking a step further than the NCLs by forming a Translational Advisory Board (TAB) of experienced nanomedicine professionals for companies to learn from and by establishing nanomanufacturing pilot lines. Finally, as we've seen above, Levy is also willing and able to explain where we are with what is to come. He does that, interestingly enough, with a reference to the advent of automobiles.

## BACK TO THE FUTURE OF MASS MEDICINE

Levy shows me a slide of Henry Ford sitting in a prototype automobile at the turn of the 20th century. The text says, "If I had asked people what they wanted, they would have said faster horses."

Levy explains that, although continuing and welcome, it's not more improvements in biology (or chemistry) alone that will change the drug landscape. "Medicinal chemistry is the art of compromise," he says quickly. "The same molecule has to be delivered and play a role in toxicity and efficacy, so you settle for the less-worse solution. However, if you have a drug like Doxorubicine and put it into a nano-liposome, you reduce the need for compromise on the molecule because the distribution and the toxicity are taken care of by the nanoparticle."

Levy notes the current (biological) view of a cancer cell with a myriad of and complicated pathways. To produce an effect in the cell, you have to make manipulations on your molecule, but the complexity is limiting in terms of time, money, efficacy, and indeed scientific possibilities. "Biology is looking for an interaction with one molecule [the target] within a cancer cell in a body of billions of cells; you never know the complexity of interactions between your drug and multiple molecules within this body," says Levy. "But look at the cell from a purely *physical* perspective; now you see identifiable objects, floating and moving in the cell as well as pillars and structures with physical behaviors. You can define physical constancy, like PH and physical mobility, temperature, pressure. You are redefining yourself and the concept of the target itself."

The implications for cancers particularly, where there may be thousands of different cells to target, are clear. Today, drugs seem to have an effect on some of those cells, but not on others; some are "killed," but others survive … and become resistant. According to Levy, this is an issue of conceptualizing within the highly variable world of biology, where every patient, even each cell, is different. "Now consider those same thousands of target cells receiving a nanoparticle providing a physical effect. That same particle will kill all the cells, with no exceptions. He adds, "It is not about *personalized* medicine anymore, but *mass* medicine."

As perhaps the *pièce de résistance*, Levy adds the dimension of version upgrades. "You may start with a nanoparticle you want to heat to 50 degrees, but soon you can improve this function to 80 degrees. Nano allows for generation after generation of product. You can then combine functionality, just like an iPhone. We can add MRI visualization to the same particle that will heat, for example. You don't do drug discovery; you plan innovation with product design. It is a completely different way to fight disease."

## THE BUSINESS FROM HERE TO THERE

The chief business officer at nanotherapeutic developer Cerulean Pharma, Christopher Guiffre, believes the drug industry will be greatly disrupted by this next generation of nanomedicine. "Five years from now I predict every Big Pharma will have nano programs," he says. Indeed, a quick Internet search associates many pharma with the word nano. Merck is one of the biggest utilizers of nanoproducts to date, and last year Pfizer signed a deal with BIND Therapeutics Inc. (BIND) to collaborate on the development of nanoparticles, called Accurins.

> *"Medicinal chemistry is the art of compromise. The same molecule has to be delivered and play a role in toxicity and efficacy, so you settle for the less-worse solution."*

So, at the same time that much of the healthcare industry seems focused on personalized medicine, nanomedicine may bring us back to the possibilities of a simpler, mass-medicine approach.

The fields of genetics, epigenetics, proteomics, and biomarkers have given us promising tools to work out our differences as biological entities and the differences in the biology of our diseases. (These tools, to a large extent, became *the* biotechnology industry.) A major reason for going in the direction of precision medicine (already evolved from personalized medicine, at least in nomenclature) was precisely because we couldn't get mass medicine to work better. But precision medicine is complicated, time-consuming, can be invasive, and extremely expensive. What if nanomedicine re-permits the treating of disease with mass-produced, singular (nano) drug products? Besides the obvious benefits to patients, profitability could skyrocket for drugmakers, and healthcare costs could be drastically reduced across the board. Just to name one area of direct cost savings, compare the size of an API manufacturing facility to a nano-manufacturing facility. (Hint: It's like comparing a huge factory to a large room, with less and less-expensive equipment.)

So all these (little) thoughts on nano surely add up to major contemplations on the future of medicine. Expect more editorial on this topic in future issues of *Life Science Leader*.

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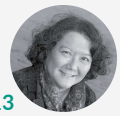
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## Panel sessions

- Protect yourself by building an outsourcing infrastructure
- Avoid the conflict by eliminating these quality agreement mistakes
- It's a global search to find the right CRO/CMO
- Understanding the impacts of FDA quality initiatives on sponsors
- Don't let an outsourced supply chain put your business at risk
- Do you have a risky risk-mitigation strategy?
- Measuring the performance of your suppliers
- Building a scalable outsourced development model
- Implementing winning tech transfer strategies
- A detailed investigation on the finances of outsourcing

1 **Chris Achar,** CEO | Genzum Life Sciences
2 **E.J. Brandreth,** VP Quality | Inovio Pharmaceuticals
3 **John Gregg,** President and CEO | BalinBac Therapeutics
4 **Doug Jolly,** SVP Research & Development | Tocagen
5 **Paul Maffuid,** VP Pharmaceutical Development and Operations | MabVax Therapeutics
6 **Pat Mallon,** COO | Polynoma
7 **Linda Marbán,** President, CEO & Director | Capricor Therapeutics
8 **Brian Mendelsohn,** Leader of ADC Chemistry Group | Agensys
9 **Terry Novak,** COO | Pernix Therapeutics
10 **Nils Olsson,** VP Chemistry, Manufacturing | Retrophin
11 **Joseph Payne,** President and CEO | Arcturus Therapeutics
12 **Philip Roberts,** VP Technical Operations | Orexigen
13 **Becky Tanamachi,** Sr. Director, Manufacturing | Halozyme Therapeutics
14 **Nicholas Virca,** President & CEO | HedgePath Pharmaceuticals

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# Why Is Takeda Focusing On Vaccines?

ED MISETA Executive Editor @outsourcedpharm

*Succeeding in the vaccines business is not easy. Low margins and manufacturing challenges make it a difficult business for any pharma company. In fact, two large manufacturers, Baxter and Novartis, recently pulled the plug on their vaccine efforts. Four of the remaining sponsor companies, GSK, Merck, Pfizer, and Sanofi Pasteur, are formidable competitors. Despite the challenges that exist, Takeda decided in 2012 to enter this global market, building upon its 70-year history of Japanese vaccine business, with plans to be the world leader by the year 2020.*

Takeda's entry into the market was an initiative pushed by Tadataka (Tachi) Yamada, who served as the company's chief medical and scientific officer (CMSO) from 2011 until being succeeded by Andrew Plump in 2015.

In an August 2013 article in *Life Science Leader*, Yamada noted vaccine development is a great business investment. He stated vaccines represent a product line not dependent on the life cycle of intellectual property, while pointing to the growth taking place in the vaccines market (increasing from $5.7 billion in 2002 to $27 billion in 2013, and expected to grow by a 10.3 percent annual rate through 2015.)

Rahul Singhvi, COO for Takeda's Vaccine Business Unit, agrees with Yamada, noting vaccines can make such a huge impact on patients' lives. After clean drinking water, immunization is an investment that can substantially improve the lives of people around the world.

Vaccines are a preventative medicine, so they are also cost-effective. The measles vaccine, for example, costs pennies. A vaccine shot early in life can prevent you from getting that disease, in some cases, for your entire life. That's a pretty remarkable intervention in someone's health.

Singhvi believes preventative medicine should be a commitment for all healthcare companies, and vaccines are a big component of that. If you make a good vaccine, it can be effective at reducing the disease burden by up to 99 percent. There are not a lot of medicines that can make that claim. And you can do this at a population level. With vaccines, you are not only treating an individual; the entire population, including unimmunized persons, may be protected indirectly by those vaccinated.

Unfortunately, there are also major challenges that must be overcome when working with vaccines. Even with the recent exit of Novartis and Baxter, the four dominant manufacturers still make for a concentrated industry on the multinational side. There are also emerging vaccine companies in countries like India focused on producing vaccines for the lowest possible price.

For Takeda to be successful, it must have a unique and differentiated strategy. "The established business we have in Japan is our foundation," notes Singhvi. "That infrastructure gives us a dominant brand in an important market, which is one of the pillars of our strategy. Another is to innovate with best-in-class products. We have acquired two companies with promising vaccine candidates. One is a vaccine against norovirus, which is the diarrheal disease that is increasingly recognized as a major problem in many settings, including day care centers, long-term care facilities, hospitals, and cruise ships. It is one of the most dominant GI bugs, even in first-world countries like the U.S., and we hope to be first on the market with this important vaccine."

The other vaccine targets dengue fever, a worldwide mosquito-borne problem. Over the last four decades, the disease has steadily spread geographically, and the growth of cities in tropical regions places an increasing number of people at risk. Singhvi acknowledges Sanofi is ahead of Takeda in that area, but he feels his company has a good candidate against the disease.

But it will take more than a good strategy to become the industry leader. First and foremost, Takeda will have to work on diseases that are globally relevant. Both

norovirus and Dengue will be important in many countries, if not worldwide. But to become a global vaccines manufacturer, the company will have to scour the world to find the best possible vaccine candidates, acquire them, and put its development and manufacturing expertise to work to bring them to market.

## Beware Of Manufacturing Challenges

In addition to the two vaccines mentioned previously, Takeda has several other candidates, including one for another mosquito-based disease, and one for Enterovirus 71, an infection of children that causes a rash illness and neurological infection, more commonly known as hand, foot, and mouth disease. Although these are all candidates the company believes it can execute on, it also wants to be careful about how many vaccines it takes on at one time.

"Developing a vaccine takes a lot of effort, and we have to be careful about balancing our focus on these products versus being too broad," says Singhvi. "We have a great virus-like particle vaccine platform that has shown a lot of promise, and it is this platform on which the norovirus vaccine is based. But it can also be used for other vaccine candidates, and we need to be prudent in how we move forward with it."

Vaccine manufacturers also need to be prepared to ramp up quickly in the event of a pandemic. Managing an organization to be ready to do so is another challenge.

"I think the H1N1 pandemic influenza outbreak in 2009 was a particularly extreme example," adds Singhvi. "Even countries like the U.S., which have enormous resources at play, were unable to bring a vaccine in time. That, I think, was a wakeup call. When you see a situation like that and realize what a virus can do, you know that it is not a theoretical problem anymore."

In Japan, as part of its pandemic preparedness process, Takeda built a massive flu facility based on cell culture, which can be quickly scaled up. Takeda purchased the technology for this facility from Baxter. The ability to quickly scale up is something Takeda refers to as surge capacity, and it gives the company enormous volume potential.

To construct the facility, Takeda received assistance from the Japanese government, which provided two-thirds of the total cost through capital investment. It was a shared risk, but done in the spirit of serving the public health and being in a position where Takeda could quickly produce large quantities of a vaccine in extreme circumstances.

The facility equates to a great opportunity for Takeda, but it also represents another challenge: How do you keep the facility "warm" during times when there is no pandemic? "That is an important consideration for us," says Singhvi. "We have to find work for that facility in order to pay the bills, since the operating costs are enormous. One approach that helps is to get into the seasonal flu business. The seasonal flu vaccine can be manufactured in the same facility that might be used for a pandemic. This is the approach we are taking, and the hope is our production management will keep the facility warm and ready to produce vaccines should we get the call."

## The Desire To Be Number One

With the challenges that exist, how will Takeda execute on its goal to be number one in vaccines by 2020? Finding the right talent is certainly critical. Since the globalization of its vaccine business in 2012, Takeda has been able to attract almost 200 talented professionals, including the president of its Vaccine Business Unit, Dr. Rajeev Venkayya. Venkayya was previously the director of vaccine delivery at the Bill & Melinda Gates Foundation, where he was responsible for the foundation's top two priorities of polio eradication and new vaccine introduction. Singhvi is another example. He started his pharma career at Merck and was part of the team that developed the shingles vaccine.

Partnerships will also be a key component of the company's success. Singhvi notes partnerships in pharma used to be nonexistent, citing his time at Merck when companies were fairly self-sufficient. Today there are many more partnerships with both CROs and CMOs, and Takeda is more open to these partnerships. Takeda will even work with other manufacturers

*"Developing a vaccine takes a lot of effort, and we have to be careful about balancing our focus on these products versus being too broad."*

**RAHUL SINGHVI**
COO for Takeda's Vaccine Business Unit

if they have competencies the company requires.

"We believe this type of collaborative partnering approach is beneficial to all companies involved," states Singhvi. "Drug and vaccine development is not a zero-sum game. We believe that by working together, we can expand the pie and create additional value for both companies. I personally feel this is a trend that is good for the industry, and others are recognizing that as well."

When deciding what parts of the development or manufacturing process should be outsourced, Singhvi believes companies need to be strategic with their choices, provided options are available. One situation where it makes sense to do so is when the company needs to get a product to market as quickly as possible. "In the old days that was unheard of," he adds, "because of the complexity involved with producing vaccines. This includes the number of tests you have to go through to get a vaccine released, as well as the volume that must be produced. With vaccines, a manufacturer might have to produce tens of millions of doses that, in the case of the flu vaccine, have to be produced and sold within a couple months."

The situation requires manufacturers to closely manage volume, quality, and the forces of demand and supply. On top of all that, there are cost pressures, because you don't have the luxury of high prices that you might find with other drugs. "When you look at all of these factors, you realize how difficult manufacturing vaccines can

be," he says. "Companies, for good reason, have been reticent in outsourcing vaccine development. However, there are opportunities where we can certainly use a CMO model for manufacturing."

To avoid a catastrophic situation, Takeda does not want to be dependent on just one facility. In some situations, the CMO being used acts as the second supplier, which provides additional security.

All of this helps manage the complexity of manufacturing, but it does not make the business any easier. After all, vaccines, like most biologics, are difficult to manufacture and require excess capacity for scale-up. Further, vaccines are part of an industry dominated by four top-10 pharma companies, and that industry constantly pressures sponsors for lower prices. So, why choose to enter the market at all, especially at a time when some pharma companies are looking for an exit?

Pharma companies are certainly not ignorant of the risks involved with vaccines. My colleague, Louis Garguilo, recently wrote two articles for Outsourced Pharma dealing with this very topic. His conclusion? Pharma companies are increasingly unable to sustain the costs of vaccinating populations around the globe. To meet the world demand for vaccines, new technologies and updated facilities are necessary. But without higher prices on vaccines, that reinvestment is not possible. Unfortunately for the manufacturers, global organizations like WHO and UNICEF believe higher prices are unacceptable. According to Garguilo, when innovators can't sustain their R&D business model, they will curtail their R&D efforts and/or exit vaccines altogether.

But perhaps Takeda will not have to bump heads with other large pharma companies. The company is not looking to invent a new vaccine for measles, DTP (diphtheria, tetanus, pertussis), or polio. It is looking for innovative vaccines that do not currently exist. That means it is more likely to be competing against the smaller start-ups and biotech companies.

"From a business perspective, I would add that vaccines are a medicine that is somewhat immune — no pun intended — from generic competition," adds Singhvi. "In the U.S., we still do not have a competitor for the MMR vaccine introduced by Merck in the late 1960s. Contrast that with the drug industry, where generic competition is a major concern for pharma. From a profitability standpoint, this is a steady business. Developing a vaccine requires a strong and long-term commitment, and these products take longer to come to market than most drugs. But once they're on the market, they tend to have a long life." L

JAMES SAPIRSTEIN
CEO of ContraVir

# ContraVir:
## MAPPING A CIRCUITOUS ROUTE TO VALUE

# THE ENTERPRISERS

**WAYNE KOBERSTEIN** Executive Editor @WayneKoberstein

**PUBLIC COMPANY (NASDAQ) - CTRV**

**MARKET CAP: $80M, but $145M fully diluted**

**CASH: $8.9M at 3/31/15**

**STARTUP DATE: February 2014**

**NUMBER OF EMPLOYEES: 14**

**FOCUS: Plucking precise antivirals, for shingles and others, from the haze of Big Pharma**

If a person can be a legend, a company should be a saga. ContraVir contains both dramatic elements — a personal path through Big Pharma to small biopharma and an extended quest through a thick forest of data to find undiscovered treasure among some overlooked compounds. When I speak with CEO James Sapirstein, he takes me on a long journey full of the intertwining twists and turns of his own career and of the company he now heads. The story gives new meaning to "follow the data."

ContraVir has two drugs now in mid- to late-stage development — one, dubbed FV-100, precisely targets the strain of herpes virus that causes shingles; the other, CMX-157, greatly multiplies the potency of its analog, the compound in Gilead's product Viread (tenofovir) against the hepatitis B virus. Both candidates have a long history of miscarried trials and misapplied data from which the company has rescued them. Sapirstein had drawn on his own history with large companies such as Bristol-Myers Squibb and new players such as Gilead.

FV-100 is an antiviral drug that originated in the Welsh company Fermavir, founded in 2000 by the compound's inventor, Chris McGuigan, at the University of Cardiff. When the company ran out of cash seven years later, it was acquired by Inhibitex, which subsequently developed two Hep C programs that overtook FV-100 as a company priority. In 2011, BMS (Bristol-Myers Squibb) bought Inhibitex and later, when the Hep C programs washed out, put the FV-100 asset up for sale. McGuigan, who by then had joined the board of the GI-company Synergy, convinced Synergy to bid and ultimately buy the asset. In 2012, Synergy incorporated ContraVir to develop FV-100.

When Sapirstein joined the company in March 2014, he inherited a wealth of clinical data generated by three Phase 1 studies conducted at Inhibitex, mainly a large proof-of-concept trial. Significantly, the PoC study was a 350-patient trial, although favorable data in PHN (postherpetic neuralgia) reduction was not prioritized — due to an arguably shortsighted analysis by the sponsor.

"The original trial design was FV-100, 400 milligrams once a day, in one arm, and 200 milligrams twice a day, in another arm, versus valacyclovir [Valtrex], the standard of care for shingles. We conducted three new statistical analyses on their data, and we saw the two FV-100 arms showed a much higher-percent drop in PHN than the valacyclovir arm. Overall, FV-100 at 400 milligrams performed almost exactly like valacyclovir. But 10 percent of the patients in the FV-100 arm needed less narcotics to treat their PHN, and there was a 39 percent reduction in PHN scores."

Until the reanalysis by ContraVir, says Sapirstein, FV-100 had always been saddled with the perception that the PoC study was a failed trial. Statistically, he says, FV-100 never reached its secondary endpoint, PHN reduction, because Inhibitex did not fully analyze the data, saying publically that it had already reached the primary virological endpoint. As a former BMS executive, Sapirstein believes Inhibitex more likely ended the trial early in anticipation of its sale to the large pharma, to concentrate on "packaging" the Hep C programs as the chief acquisition asset.

ContraVir took the reanalyzed data and reached out to the FDA for support in designing a new, Phase 2b trial for FV-100, this time reversing the primary and secondary endpoints so that PHN reduction became number one, ahead of decrease in viral load. Otherwise, the trial

In less than 24 hours after the company submitted its protocol proposal, the FDA committee granted the company a Type B meeting.

# FV-100 REBORN – DANCING WITH FDA

### FV-100 REBORN – DANCING WITH FDA

ContraVir's CEO James Sapirstein is out to ruin the FDA's reputation – the negative one too often repeated – that the agency just doesn't care. In this case, the do-over clinical development of the company's antiviral shingles drug, FV-100, has the regulators excited and all too willing to help, and the company's main challenge is matching speeds with their guidance designing the drug's new Phase 3 trial, which began in May 2015. Reversing the original endpoints in the former sponsor's Phase 1 proof-of-concept trial, ContraVir's new trial places reduction of postherpetic neuralgia (PHN) ahead of viral-load reduction as the drug's lead indication.

### WHY DO YOU THINK THE FDA IS GIVING FV-100 SO MUCH SUPPORT?

SAPIRSTEIN: We're not going after just another me-too indication. This will be a disease-modifying indication, which no other drug on this planet has for shingles. There is not one other drug indicated for PHN. So we're the only game in town. That is exciting for the FDA's antivirology division, and they are always very cooperative with truly novel agents like FV-100. From the days of HIV, I remember, this division would accelerate approvals for truly new drugs. They work with you, they want to see you bring something to market. They don't chastise, they recommend. When they granted us a Type B meeting, they said they are bringing in people from the pain division, as well as from the different stats divisions. I believe it is an effort to say, "You've done some great work on reanalyzing the previous Phase 1 data; this is what we recommend on the protocol."

### DID YOU ANTICIPATE THE AGENCY WOULD WANT TO ACCELERATE THE DRUG?

SAPIRSTEIN: We didn't ask to go into Phase 3, we just wanted to meet with them, but we were hoping they would allow us to go into Phase 3. And quite frankly, for us, the worst-case scenario was that they would tell us this is a Phase 2b trial. Our hoped-for scenario was for the FDA to say, "You've already had over 350 patients receive this drug, your safety data base is pretty complete for Phase 2, and you plan on going into 825 patients on the next trial, a fairly large study. We agree in principle with what you want to do. Here are some changes and some suggestions we're making for you, from a statistics perspective of types of patients, but we're going to let you go into Phase 3. But you need two pivotal trials just like any other product." For me, the grand slam would be they tell us, we like what you're doing, we'll let you go through accelerated approval with one trial, and you can move toward filing an NDA once you reach the middle of this trial. We're a tiny little company, and we just resuscitated this program about a year ago, so we're very pleased that the FDA allowed us to initiate a pivotal Phase 3 in June. We will likely have to complete a second pivotal trial as well, but the proposed plan for clinical development of FV-100, agreed to by the FDA, significantly shortens the development pathway for FV-100. This will save ContraVir considerable time and money.

> "We might surprise people with another Phase 3 asset as early as 2016."
>
> **JAMES SAPIRSTEIN**
> CEO of ContraVir

was essentially a doubling in size of the Phase 1 PoC, with 600 patients. As for the virological endpoint, total load reduction may not tell the whole story. Sapirstein says FV-100 differs from all other anti-herpes drugs in not being "pan-herpetic" — it does not kill all strains of herpes like a broad-spectrum antibiotic kills a wide swath of bacteria species. Instead, ContraVir's drug targets the shingles-causing strain specifically, varicella zoster, and it works in the dorsal root ganglion — possible reasons for its apparent effect on PHN in the early trial, he suggests.

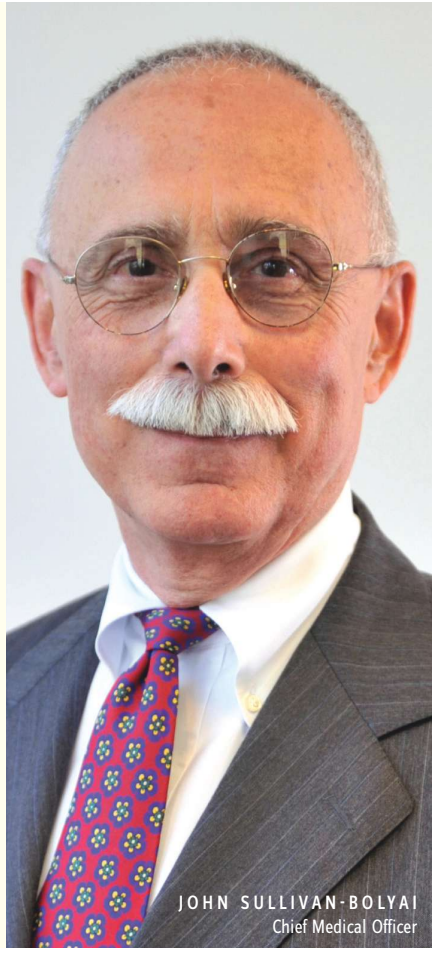
To make sure the company could match speeds with the regulators, who were now enthusiastically supporting the program, ContraVir assembled a team of clinical development experts. According to Sapirstein, Nathaniel Katz, now on its scientific board, is one of the top PHN people in the world, having chaired or served on eight FDA pain-related advisory boards. Katz and Heidi Jolson, a former FDA director, helped write the Phase 2b protocol. "What kind of language should we write this in so it's crystal clear to the FDA what we want to do? There's not a better person to ask than Heidi Jolson," says Sapirstein. The advice from Katz and Jolson included

## THE CHIEFS OF CONTRAVIR — FROM EXECS TO ENTERPRISERS

ContraVir has only been in operation since February 2014. Though it was incorporated in 2012, it lacked sufficient cash until then. Industry veteran and former Big Pharma executive James Sapirstein joined as the company's first CEO a month later. Chief Medical Officer John Sullivan-Bolyai hails from Idenix, purchased by Merck, where he worked for only two weeks. Before that, he had been in the industry for more than 25 years, including several years at Roche, and before then at Valeant.

Sapirstein has 31 years in the pharma business – 17 in Big Pharma, including Eli Lilly, Roche, and Bristol-Myers Squibb. For BMS, he worked extensively in Africa and Asia, as part of the company's efforts in HIV. After that, he came back to the United States and served as the company's head of international infectious diseases. Then he was recruited by Gilead where he stayed for several years, until 2002, when Serono hired him as general manager heading its metabolic and endocrinology division. Because of his performance there, mostly cleaning house, he says, "someone convinced me that I should be a CEO." Before going to ContraVir, he led Tobira Therapeutics and Alliqua, both of which enjoyed considerable success.

He started Tobira while doing a consulting stint at Domain Associates, working with the firm's general partner Eckard Weber. He left five years later after Tobira was named New Jersey Bio Company of the Year in 2010. "I had a run-in with one of our investors who thought we should have sold the company. I tried to explain it was 2010, and no one was buying any assets right then unless it was in Phase 3." He then struck out on his own, attempting to purchase NitroMed before joining Alliqua, which he fashioned into a wound care company, then left after landing a lucrative licensing deal with Celgene. He was finally attracted to the ContraVir start-up because of his background in anti-infectives.



JOHN SULLIVAN-BOLYAI
Chief Medical Officer

more than writing style, of course; a typical missive would be to use the proper precedent and an appropriate data set to support a given point.

The advice must have worked. In less than 24 hours after the company submitted its protocol proposal, the FDA committee granted the company a Type B meeting — one presuming the protocol's approval — to discuss how the company should address the practical implementation of the Phase 2b trial. Later, the agency told ContraVir it could go directly to a Phase 3 trial using the same protocol, greatly accelerating its clinical development, regulatory review, and possible approval. The Phase 3 trial began in May 2015.

On the same day ContraVir heard the good news back from the FDA on FV-100, Dec. 18, 2014, it received a second tiding of joy: an effective patent extension for its Hep B drug, CMX-157, which it had licensed from Chimerix in late 2014. According to the company, CMX-157, as a prodrug of tenofovir, is 200 times more potent than the currently marketed compound (Gilead/Truvada).

Sapirstein has a personal connection to Gilead and Viread, having led the flagship product's global launch there. He says he also has great plans for CMX-157, presumably as a second-generation form of tenofovir, for use as a common constituent of many different Hep B and HIV regimens.

"I believe CMX-157 will catch some people by surprise," he says. "Right now it's a Phase 2-ready asset. So we're a tiny company with two late-stage assets, with one going into Phase 3 in the middle of this year, and if things go right with 157, we might surprise people with another Phase 3 asset as early as 2016."

Sometimes, building an enterprise around a key asset requires taking a less than straightforward route to securing asset value. ContraVir mapped its own course, however circuitous, toward its goal — making use of sheer human talent and experience to mine a solid vein of data and support its claims on a novel product. If it can accomplish a similar feat with its second product, its building plans could expand by at least another exponential power. L

# INDUSTRY EXPLORERS BLAZE ON

**WAYNE KOBERSTEIN** Executive Editor @WayneKoberstein

*The stories of longtime leaders, still active in the industry, sharing their historical perspectives on life sciences industry innovation*

## This Month: Pioneer & Present Force – David Hale

**A consuming interest, plus a yearning for independence — that's how the journey to entrepreneurial biotech begins. David Hale had been thoroughly ensconced in traditional pharma when a particular assignment awakened a new passion in him.**

It was for a new technology already used in Becton Dickinson (BD), his company at the time, for laboratory experiments: monoclonal antibodies (mAbs). But neither BD nor any other company had taken the platform any further, and Hale saw a vast potential for it, starting with human diagnostics. Still, so far he had done quite well on the management track of J&J and BD. And in his position as head of a BD division, he had sworn off answering calls from recruiters.

Then the phone rang. Hale's assistant was out of the office, so he picked up the phone on impulse. In a confluence of chance and curiosity, Hale's fate was thus sealed. The call set him on a path that would lead him from the comfortable executive suites of New Jersey to a trailer-office start-up in sunny San Diego.

Since that time, David Hale has become an icon of the entrepreneurial business known mainly as biotech, having helped create the industry's start-up model. He not only made the transition from Big Pharma to little biotech decades before the current wave of converts, but also affected the very definition of the model he embraced. From his initial start-up experience at the first San Diego biotech company, Hybritech, to the some half-dozen companies he is now involved with as an executive or board member, Hale has been in the thick of the sun-glazed industry with its roots on the coast of California. Like William Comer, featured last month in our initial Industry Explorers Blaze On, Hale sees risk-taking as an essential element in innovation, and luck as well — the kind of luck that led him to take that fateful phone call.

## Changing Coasts

By the time Hale took the call, he had already seen the traditional pharma industry practically turn itself upside down searching for new blockbusters. The Orphan Drug Act was relatively new, and companies used it pretty much as it was intended — to develop drugs for well-identified orphan conditions that promised little in market return. Every company wanted the next Tagamet or Motrin, then prescription drugs that drove massive scrip-writing pushed along by direct-to-consumer advertising. If that meant a mad rush to buy and absorb whole companies — many of them historical bastions of then Big Pharma — so be it.

The survivors, the few companies left once the most vulnerable assets were gone, then struggled for many years with integrating what they had absorbed, pumping money into R&D and sales despite a steady decline in their return on investment. Meanwhile, the now mega-sized companies continued to act according to their previous tradition: slowly, carefully, and with a core aversion to risk. Shunning the wild-eyed experiments of the long-haired professors out West, the pharma establishment forfeited much of the new science and many of the new technologies that would prove most innovative in the decades to come. The golden example was monoclonal antibodies.

"I had a great career at Johnson & Johnson," says Hale. "I had great opportunities to be involved in a number of aspects in commercialization and pharmaceutical products there. Then I went down to Becton Dickinson to run a division that was primarily microbiology diagnostic products, where I got very interested in monoclonal antibodies." His interest was not purely academic, however. "I had a strong feeling monoclonal antibodies were going to revolutionize diagnostics."

Immediately out of college with a degree in biology and chemistry and an enduring interest in science, Hale first pursued a detailing job in pharma, but his lack of sales experience, and his singlehood, stood in the way. This was the early 1970s, and pharma reps were expected to be solid family men, as well as professionals with established careers and advanced degrees, often in pharmacy. Hale found it easier to land a job selling industrial chemicals, where he developed a unique technique for persuading reluctant production managers to test and ultimately convert to his products.

"I convinced some production managers to let me come in on a Friday evening, clean out their tanks, and do a produc-

*The call set him on a path that would lead him from the comfortable executive suites of New Jersey to a trailer-office start-up in sunny San Diego.*

tion run on Saturday substituting the chemicals I wanted to sell them. Of course, the deal was, if my chemicals didn't work better than the old ones, I would have to reclean the tanks before production restarted on Monday. But if they did work as I promised, I left the line as is, and production resumed with the new chemicals and an order for continuing supply. Although I spent many weekends inside empty chemical tanks, I ended up converting a lot of customers to our chemicals."

He was pleased with how things were going — management was noticing his sales performance and his commissions were growing. But after someone he knew, a production manager at a customer's plant, fell into a filled chemical tank and suffered severe burns, Hale decided to make another run at pharma. An interview at J&J's Ortho pharmaceutical division in 1971 led to training in New Orleans, followed by a sales job in Jackson, MS, with the entire state as his territory.

Soon, Hale brokered a deal with a large statewide clinic that resulted in the largest clinic order Ortho had ever experienced. As the news of his coup spread throughout the company, it reached the attention of management in the New Jersey headquarters, and a subsequent promotion returned him to New Orleans, where he had trained only a year before, for a new job as a sales trainer.

"I was about 24 at the time and now training people who were significantly older than me." Nine months later, a marketing executive came to work with him in his territory and then offered Hale a product manager position back in the New Jersey office. Still single, Hale packed everything he owned into his car and drove there. He was the first single person in the company promoted from field management to such a position.

Hale immediately engaged the office politics of the time. On his first day, his to-be manager resigned. "It then became my objective to make sure the company would not feel the need to replace this person. I worked 12 to 16 hours a day, every weekend, and sometimes even more, and was able to cover all the bases and do things my way without a new direct manager over my head."

Hale had also realized that no one ever rose very high in the Ortho organization without working for a time in sales management. That opportunity came along a few years later when he was promoted to head sales in the area around Pittsburgh, where, at the time, Ortho had the lowest market share of any division in the country. He put together and executed a plan that increased the share significantly and, a mere 10 months later, returned to New Jersey with a promotion to direct the marketing of Ortho's main product line.

Two years later, Hale took over as director of marketing for Ortho's dermatology division, where he was made certain promises if the unit hit certain profit and revenue goals. But, perhaps because the company never expected the goals to be met, he says, the promises were not kept when they were. He began to look around.

A recruiter led him to a contact at Becton Dickinson, who Hale also happened to encounter and meet with during an industry conference. Their conversation resulted in Hale's decision to leave J&J and move to a BD division in Maryland to be VP of sales and marketing in the BBL Microbiology Systems division.

In 1981, Becton Dickinson asked all of its divisions to evaluate possible new applications for monoclonal antibodies. Hale's unit submitted a report saying mAbs would be the key technology in future diagnostics and urging the company to make a major commitment to them. "We said we can be a real leader, because Becton Dickinson already had a position in monoclonal antibodies as research tools." The plea was in vain, as it turned out. "BD determined there were characteristics of monoclonal antibodies that weren't suited for diagnostics and decided not to pursue them in a significant product development," Hale says.

Soon thereafter, one afternoon, his phone rang. "I got a call from a headhunter about Hybritech, this tiny little company out in San Diego that was applying monoclonal antibodies in diagnostics. I told him I wasn't interested, but he had a unique approach. He asked me, 'How's the weather there?' And I said, 'Well, it's sleeting and snowing.' He said, 'I'm standing on the beach in San Diego, and it's 75 degrees and sunny and beautiful. Wouldn't you and your wife like to come out on a vacation, and you can just spend a couple of hours at Hybritech?' I agreed to come out and visit with them, and I saw them doing things with monoclonal antibodies that BD had said couldn't be done. There was proof right there on the laboratory bench that they worked in assays, and so that was what won me over."

By this time, Hale was not only married but the father of three children all under five. A move to California would be more than an adventure; it would be disruption, in all senses of the word. But the move it would be. His first visit to the company proved decisive. Telling his wife about the visit later, he avoided describing Hybritech's temporary headquarters, a trailer in a parking lot, or its use of rented

*"Developing any new technology is going to take a long time. It's not for the faint of heart."*

**DAVID HALE**
CEO of Hale BioPharma Ventures, LLC

lab space while its new facilities were under construction, and simply shared his excitement about the opportunities he saw. In the end, he made a move that hinged on a somewhat random phone call and the simple urge to be where the action is. Hale joined Hybritech initially as vice president of marketing and business development and later became president and then CEO.

"My friends thought I was absolutely crazy, and probably in retrospect I was, but I was convinced of the potential for monoclonal antibodies, and monoclonal antibodies became exactly what I thought they would be — the cornerstone of diagnostics and eventually therapeutics."

Hale says two people in particular had a "very significant influence" on his decision to join Hybritech — Howard Greene, president at the time and later chairman, and Thomas Adams, chief technical officer, head of R&D, who had come to the company from DuPont Laboratories. But a big turning point was a dinner with Thomas Perkins and Brook Byers, founders of the venture capital group Kleiner Perkins Caufield & Byers and the initial investors in Hybritech. "In all of my business career, that was the most intense business dinner I ever had. It was like being interrogated, and I thought at the end of the evening, 'No way am I going to get this job, even if I want it!' It turns out I did a little better than I expected."

He was part of a management team that surprised the world and helped jumpstart an entirely new industry in new territories, geographic and business, where no one expected it to happen. Making history, Hybritech became a leader in the mAb space, a David challenging the diagnostics Goliath, Abbott, and was acquired by Eli Lilly in 1986.

## TAKING IT BACK — OR FORTH?

The sale presented Hale with another hard choice: Should he now return to the once-familiar fold of Big Pharma or remain in the small-company world on the West Coast? The decision was all the harder because it was too easy; in other words, J&J wanted him back, and the big company had made an offer that was obviously too attractive to turn down. So of course he would take it.

"I went back east to talk with Bob Wilson, who would become J&J's vice chairman, as well as Jim Burke, chairman, and Dave Claire, president, and they wanted me to come back and run Ortho's diagnostics business," Hale recalls. "They convinced me I should return to J&J, and I felt committed. But when I had returned to San Diego, enjoying the weather that evening, I told my wife, 'I'm just not sure I'm cut out to be in a big company any more. I really like having the opportunity to work in a small-company environment. We essentially talked about it all night and the next morning, and I spent another day thinking it over, then I called J&J and said I'm not going to come."

Hale took immediate action on his decision, getting involved in two small companies, Gensia, which was in preclinical development of its lead cardiovascular drug, and start-up Viagene, then setting out to develop a gene therapy for HIV. "I really liked being in an entrepreneurial start-up environment where decisions could be made quickly, where the decision process involved only a few people and not a small army, where you had to wear lots of hats, and you could make a difference pretty quickly. The start-up, entrepreneurial environment was the one I wanted to continue working in."

Although small companies mirror large ones in many respects, starting with management structure, Hale still sees in them a relative lack of bureaucracy. But sometimes the "nearness" of everyone in a small corporation can bring pain that a much larger one would readily absorb. At Gensia, one of Hale's toughest duties was laying off 300 people in one day following a failed Phase 3 trial. "It was just one of those things you hope you never have to do, but almost no one goes through their career without being involved in that at some point," he says. "Our board was very supportive. They thought we had done the right study and done it well, and the company had to move forward, but in a different format."

Gensia had encountered the fabled Valley of Death, where products in late-stage development often perish. It is an area of risk all small-cap companies must traverse — though some evidence suggests the larger the cap, the higher the chances of clinical success — yet it is also the kind of risk Big Pharma prefers to avoid or at least hedge against with conditional licensing deals.

Hale agrees with Bill Comer's maxim, "Without risk, there's no innovation." And he adds his own observation: "You can't make a product work. Sometimes the risk is going to end up in a failure of the product. That doesn't mean that the company has been a failure or that the people involved are failures. You may have conducted the absolute best and right clinical study, but you can't make the product work. You can just design

the environment to evaluate whether it works, and that's where you have to focus your efforts, but you're not always going to win."

Monoclonals offered the same lesson when first introduced as therapeutics; Centocor, which later formed the core of Janssen Biologics, almost dissolved entirely after its drug Centoxin washed out a pivotal trial in septic shock. Hybritech chose the diagnostics path first and had earlier research under way in mAbs for oncology, but left the septic shock battle to Centocor and its rival Xoma, whose product in the same indication also failed.

"But we were developing technology — the first technology for humanizing antibodies, chimeric antibodies," he explains. "When Hybritech was acquired by Lilly, some of that technology went to Idec and in a peripheral way helped Idec develop Rituxan, the first mAb therapeutic in cancer. And it became a huge draw for other oncology mAbs. We were working with monoclonal antibodies in the cancer area in the 1983-1984 time frame, and it took a long time to understand how they worked, that you had to use a humanized antibody or chimeric antibody, and then how to dose them. It was 1997 before Rituxan was introduced, and today mAbs are probably the largest segment, by dollar volume, in the pharmaceutical industry." Indeed, a whole new use of monoclonals in oncology has emerged with the new checkpoint inhibitors and other immunotherapeutics.

"Developing any new technology is going to take a long time," says Hale. "It's not for the faint of heart. Some mistakes will be made along the way, and there will be some hard lessons you must build upon to meet with success."

One lesson he learned: the more exotic the technology, the longer it will take to develop. Viagene is a case in point, he says. The company began with a gene therapy platform in 1987, and it was acquired by Chiron in 1994, but only recently has gene therapy produced a host of interesting new drugs in development. "I believe the same principle applies to technologies such as RNAi; eventually, some very exotic drugs will come from them, but it won't happen as fast as we would like it to happen."

## MENTOR OF CHOICE

Hale continued to found, run, and often sell new companies in the decades that followed. Among the many he cofounded were SkinMedica, Evoke, CancerVax, and Somaxon. He was CEO of CancerVax and Women First HealthCare. He was chairman of the public companies Somaxon and Santarus until they were sold. He is now chairman of two public companies, Conatus and Biocept, and the private companies Ridge Diagnostics, MDRejuvena, Advantar Laboratories, Agility Clinical, Recros Medica, Colorescience, Skylit, and Dermata Therapeutics. And he serves on numerous boards, and he's active in the nonprofit world, for example as cofounder and director of BIOCOM/San Diego. His own firm, Hale BioPharma Ventures, is dedicated to forming new biopharma, specialty pharma, diagnostic, and medical device companies. Whether in a business relationship, nonprofit educational setting, or plain old personal mentoring, Hale tries to pass on the valuable lessons of his experience. "One of the things I really enjoy is working with young, and in some cases, first-time CEOs. That is a very rewarding experience, helping them grow and develop and become better CEOs."

Hale offers a useful contrast to the long-held stereotype of the scientist founder, wanting to see every product through to the market. His interest in science and ability to master scientific concepts was long established, but he also came into the start-up culture of biotech with a great deal of business acumen.

"I always try to involve myself with people who have a deep understanding of the science, and I provide the business input, the commercial side. Is there really a market opportunity for this product? What would we have to do to develop the product to address that clinical need? Otherwise, we leave basic research to the NIH and academic institutions that do basic research. In my opinion, basic research is not in the purview of the companies I am generally involved in. I'd rather establish a collaboration with an academic institution where it continues to do what its people are really good at, research, and I hire people who are good at development. A good marriage is when you can combine those efforts."

Hale has other basic advice for new company founders. He emphasizes the importance of building a high-quality management team, board of directors, and scientific/clinical advisory board, including regulatory experts. Next, be prepared to operate virtually, at least until you have sufficient proof-of-concept to overcome the contemporary resistance by venture capitalists to fund early stage companies. "When I was first involved, and even through the early 2000s, venture capitalists were investing in Series A or

> "I REALLY LIKED BEING IN AN ENTREPRENEURIAL START-UP ENVIRONMENT WHERE DECISIONS COULD BE MADE QUICKLY, WHERE THE DECISION PROCESS INVOLVED ONLY A FEW PEOPLE AND NOT A SMALL ARMY."
>
> **DAVID HALE**

even earlier in companies, but a lot of VCs have pulled back and there is just less overall money."

Another change among VCs to which new companies must adjust: Formerly, a company presentation might consist of how management plans to build a company from its core technology. Today, says Hale, that is more the exception than the rule. "Most venture capitalists want to have a discussion about your exit strategy and at what point in the development process you will have created enough value to accomplish that exit."

Hale also acknowledges the possible alternative to exit — full integration. More companies are avoiding deals that prevent them from growing independently all the way into the market. "If you can reach the market with a small, specialized sales force, and the clinical development program is feasible, you might consider integration," he says. "Many such companies are looking in the orphan disease area, where the clinical trials are fairly small in the required number of patients, and it could take a reasonable amount of money to get to commercialization, as well as a reasonable amount to call on the doctors needed for commercial success. Some of those situations still exist out there."

## THE CURRENCY OF CHANCE

Virtuality and orphan drugs coincide in a need Hale identified for one of his latest ventures, the CRO Agility Medical, formed with Ellen Morgan, among those whom Hale once had to lay off at Gensia. A Pfizer alum, Morgan recovered from Gensia by starting her own CRO, Synteract, which she ran for many years. But a few years ago, she called Hale wanting to start a consulting and clinical trials management group specifically for orphan drug candidates.

"Some of the things I do now are with people I've worked with in the past, and Agility is one of those," he says. "Ellen Morgan was head of our data management at Gensia and founded and had good success with Synteract. I told her she had a great idea. So she and I started Agility."

Hale is not one to stay in one place for very long. He is on board with each company for a certain tenure, but he always seems to have a lot of irons in the fire — a sign, he says, of how his career has evolved, but also of where he wanted it to go. "I do like being involved in a variety of companies focused on different products, in different therapeutic categories, in different market segments, and with different market opportunities. Most of the companies I've run were eventually sold to big companies such as Allergan or Amgen, even those I may have been with for more than a decade. The challenges, opportunities, and business are all different in each company, so it keeps things very exciting and challenging."

He says another currently exciting project for him is Conatus Pharmaceuticals, working in the liver disease area, primarily cirrhosis. After a validating trial for its lead compound, the drug must now go through further clinical studies and the regulatory process. He is also involved with a molecular diagnostic company in cancer, Biocept. "Many studies now have shown that, as the tumor progresses, it does not remain the same tumor as when it was first biopsied. So I am convinced that eventually, as patients progress, physicians will use 'liquid biopsies,' or blood samples, rather than the original tissue samples, to diagnose and monitor patients and select appropriate therapy."

Hale is also targeting a new business niche: "patient-pay" healthcare opportunities. As the reimbursement environment keeps getting tougher, some businesses will deliver nonreimbursed medical products to patients who can afford to pay for them. Particular areas include dermatology and plastic surgery, where many patients already pay full measure, and the commercial suppliers never worry about CMS (Centers for Medicare and Medicaid Services) reimbursement.

Meanwhile, Hale remains centered on the implications and implementation of the virtual model by start-up life sciences companies. Beyond general principles, he offers some practical counsel: "It is very critical in the virtual model to have a network of people you can call on to help you with formulation development, toxicology planning or implementation, and clinical development — people who are not employees but are part of a team, whom you pay based on the hours they work. The problem with the virtual model is you never have enough resources to do everything you want to do. Sometimes you have to sprint ahead and wait awhile. If you had appropriate funding, you could move development programs ahead much quicker."

Could Hale do it all over again — start where he did 40-some years ago and build so many companies — given current conditions for the industry? His reply gives more weight to chance than conditions. "I kind of stumbled into the experience with Hybritech," he says. "If I had been out to lunch when that call came, I would've probably stayed in Big Pharma. At least, I'm not sure if I would have made the move to a small company. Looking back, it was pure luck that I happened to be there when that call came in and I took it. But if I were young again, if the idea were right, and the plan were right, I could still go out again and find an opportunity to start a company."

So is it chance and luck, or is it desire and opportunity that makes an entrepreneur the likes of David Hale? I would place my bet largely on luck, because it never gets the credit it deserves. But I would count on the will to win as the one irreplaceable ingredient for the explorer's success. L

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# Building A Narrative: Develop Emotional Connections To Raise Capital

**GAIL DUTTON** Contributing Editor

*For 55 years, comedian Jerry Lewis hosted Labor Day Muscular Dystrophy Telethons featuring "Jerry's Kids," the poster children who made muscular dystrophy real for millions of Americans. By creating an emotional connection with the audience, those telethons raised more than $2 billion.*

Companies seeking to raise funds need to create an emotional connection with their audiences, too. Without it, they may not get the monies they need.

A common problem, according to Zayna Khayat, lead, MaRs Health at Toronto's MaRs Discovery District, is that "Scientists take a very rational approach and let the data speak for itself. They think their value proposition is so obvious that investors hearing it would naturally write a check."

In reality, when pitching investors, "You have only about 30 seconds to hook an audience," Khayat says. Setting that hook requires an emotional strategy that focuses first on why an innovation matters. "That glues them to you and your company," she says.

Khayat recommends telling the story from the perspective of a patient. MaRs start-up Profound Medical, which announced a $30 million reverse takeover last spring, begins its pitch by discussing the standard of care (radiation or surgery) for localized prostate cancer. "The men in the audience cringe," says Steven Plymale, CEO. "Then, when we describe our alternative, transurethral ultrasound ablation technology, there's an aha moment."

At that point, the audience is hooked. Plymale can then discuss why he believes this approach is better than the standard of care. Afterward, he addresses elements such as how the technology works, the Profound Medical team, and how the company plans to use the funding.

Discussing prostate cancer can make a visceral connection with potential investors, but many other conditions lack such impact. Nonetheless, an emotional link can be made.

"Making an emotional connection isn't just about discussing unmet need or market potential; investors know about both of those things already," points out Carin Canale-Theakston, president, Canale Communications.

HIV is a good example. Scientific advances have transformed HIV from a deadly disease to a chronic disease that allows patients to live relatively normal lives. To make the necessary emotional connections with potential investors, companies working in this space must show that their work makes a notable improvement to the standard of care, such as addressing the cause of the disease rather than just its symptoms, dramatically lowering medication costs, or significantly improving quality of life.

## LESSONS FROM SCHEHERAZADE

One of the common mistakes young companies make is presenting too much detail too early, Khayat says. "Show credibility, but not the Western blots (a powerful technique to analyze protein expression) in six-point font or every paper that team members have written. Overindexing comes at the cost of not doing other things," she cautions.

To counter the urge to present all the details in the first meeting or two, Canale-Theakston advises her clients to tell their stories like novelists. As an analogy, consider the story "Arabian Nights" (also known as "One Thousand and One Nights"), in which the bride Scheherazade enthralls her husband, the king, with nightly stories. By hooking him with her compelling narratives and always reserving some details for their next meeting, her execution is delayed night after night. Eventually, the king becomes fully invested in his wife, and the tales are no longer needed. Scheherazade lives, and so will companies that learn the art of narrative pitches.

In adapting this model for business, "Think of it as a funnel approach," Canale-Theakston says. "Start the narrative at a high level. Then go deeper based upon

your audience's responses. Let them guide you."

## PRESENT THE RIGHT DETAILS FOR YOUR AUDIENCE

Once the audience is hooked, presenters can begin to address the details of the science, the company, and its plans. Too often, they omit critical details in their desire to showcase their science. For example, they often neglect to explain how they will use the funds they are seeking. As Khayat asks, "Why do they want this particular amount? Where, when, why, and how will they spend it?" She recommends presenting a flexible five-year plan that answers those questions and outlines the company's development strategy.

Companies also tend to overlook the total addressable market. "They present the total market potential, but not the percentage of that market they realistically can capture," Khayat says. The addressable market share is based on the company's distribution channels as well as upon its differentiation from competitors or the standard of care.

At device manufacturer Profound Medical, Plymale also outlined the product's regulatory and reimbursement strategies in his pitches. "Reimbursement and regulatory strategies go hand-in-hand. If you don't understand reimbursement, commercial results could be disappointing," he says.

As Canale-Theakston points out, "Investors should have an appreciation of the company's strategy to generate a return on investment. Showing how to create a return on investment doesn't necessarily mean selling product, however, because most early-stage companies will never reach that point." Therefore, talk about the potential to be acquired or to partner with others.

## END STRONG, BE COMPELLING

"In addition to a compelling opening and engrossing content, your story needs a closing that will grab the attention of your audience," Canale-Theakson says. What makes a good closing is being company-specific. It may be good data from a just-completed clinical trial, a patient, or physician discussing the value of the innovation, or even an efficient burn rate with the money raised to date. Whatever it is, it must give the audience a strong reason to open their checkbooks.

The purpose of the initial pitch is to get a second meeting. Presenting all the information at once thwarts the subsequent encounters that are necessary for the parties to get to know one another, learn the personalities and working styles, perform due diligence, and assess the value of a potential match.

## IF YOU'RE GOING TO USE POWERPOINT, USE IT WISELY

"I've never heard investors say a presentation was too short or too simple," Canale-Theakston says. "Entrepreneurs often use PowerPoint as a crutch. CEOs will work on PowerPoint presentations for hours, without thinking about how to speak to the slides," she continues.

Many entrepreneurs also make the mistake of pulling graphs from their research. The result is small, difficult-to-read visuals. Instead, she says, "Pull out the one point that matters, and make it the title slide."

Plymale took that a step further by including a 60-second animation. "It streamlined the explanation of the technology," he says.

## WHO PRESENTS?

"Investors don't invest in PowerPoint, they invest in you!" Canale-Theakston stresses. So, although Joel Marcus, CEO and founder of Alexandria Venture Investments, says presentation style is irrelevant to him, others may not be so forgiving.

Khayat is adamant that an engaging style matters. "The founder or CEO shouldn't necessarily make the pitch if they are perceived as boring or out of touch with the market. Companies can maximize their chances of getting a second meeting by choosing a vibrant, knowledgeable representative to make the presentation," Khayat says.

## YOU'RE SEEKING PARTNERS, NOT JUST CASH

Although raising money is the goal, Plymale advises entrepreneurs to understand they're actually seeking partners and collaborators. "They'll be married to you for a while, becoming very involved in the oversight of the company."

His presentations, Plymale says, "were about making sure potential investors understood the long-term vision of the company. They were about creating a long-term partnership involving significant money and a fair amount of risk." Therefore, Plymale advises companies to perform due diligence on potential investors.

As early as possible, determine their investment strategy, equity position in their investment, involvement in management, and how those positions affect the ability to attract funding from other companies in the future. This is particularly important as companies move from angel to venture capital funding.

The goal of venture capitalists is to translate innovation into the clinic in a way that garners a significant return on investment, Marcus emphasizes. "Very-early-stage innovators don't always understand that. We're not here to fund basic science."

## SEEK INVESTORS WHO FIT YOUR COMPANY

"Cold calling potential investors doesn't work well," Canale-Theakston says. "Spend time to understand their investment criteria and what and where they invest." She advises studying potential investors' websites and portfolios. "The portfolio is the best example of what they do."

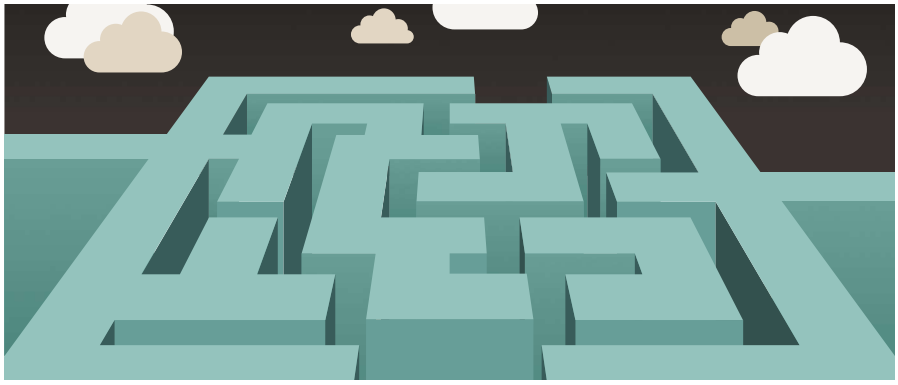
Studying investors entails knowing not only their areas of therapeutic interest, but also whether they prefer early- or later-stage investments and how they define those terms. "Understand that 'early stage' doesn't always mean 'early clinical stage.' Many companies are advancing compounds that pharmaceutical companies have had on their shelves. They're still considered early stage, but are very different from unproven compounds," Canale-Theakston says.

Plymale says he pitched Profound Medical's story 217 times. "Our message changed as we moved from private to public transactions," Plymale says, and also as it approached nontypical investors. For example, he once pitched an oil and gas investment group that wanted to expand into healthcare.

Regardless of the potential investor, "Taking the narrative from good to compelling is about engaging the audience," Canale-Theakston says. Go beyond empirical evidence to discuss what your innovation means to patients or physicians, why that matters, and why your company's approach is best. By first capturing their hearts, you may also capture their minds. L

# Alzheimer's Drug Development: Not An Easy Path To Pursue

**E. TERESA TOUEY** Contributing Writer



In the past decade, Alzheimer's research has failed to produce a new drug addressing the progression of the disease, despite the resources invested in high-profile clinical trials. A July 2014 UBS study outlines today's marketplace:

> *The amyloid-beta (AB) hypothesis remains the key target for pharmalogical intervention seeking to slow down [Alzheimer's] disease progression. Billions have already been spent on failed trials, and thus, little is reflected in share prices for compounds in clinical development across the industry.*
>
> *The pursuit of the AB hypothesis as a target for pharmaceutical intervention has been a costly and so far unsuccessful endeavor for the pharma industry, with at least six failed Phase 3 studies involving over 12,000 patients at costs likely exceeding $2.5 billion.*

Meanwhile, the four FDA-approved drugs prescribed and sold on the market treat the symptoms, not the cause, thus only slowing the progression of the cognitive decline. Given the financial community's all-too-clear memories of the Alzheimer's clinical failures of the past, companies seeking to raise capital to develop new drugs for this condition must overcome increased investor skepticism.

But some biopharmas in the Alzheimer's space are proving to be outliers of current market woes, taking other pathways to successfully move their drug candidates further along into clinical trials, while at the same time, securing financing to reach their next milestones. Anavex Life Sciences Corp. is one such company.

## THE CHALLENGES OF ATTRACTING INVESTORS

Before arriving as Anavex's president and CEO in 2013, Christopher Missling, Ph.D., MBA, spent two decades in managerial roles at Big Pharma companies, including director of financial planning at Aventis as well as the CFO and officer of two other biotech firms (Curis and ImmunoGen).

Missling was excited about the opportunities and change he could potentially affect by taking on the top executive role with Anavex. At the time, the company was in a period of managerial transition (Missling was offered the reins by a company founder seeking fresh leadership for Anavex), and there were financial constraints facing the small biopharmaceutical firm (a priority need for additional capital injections at that time). Intrigued by the company's promising, early-stage Alzheimer's drug candidate, which had shown potential to prevent, halt, and/or reverse Alzheimer's, Missling also felt a personal connection to the company, having witnessed the impact of the disease on his own family.

"It was a unique opportunity. I had the choice to join several companies, but I was impressed by Anavex's work in the area and joined because of its strong potential to make a difference in the lives of Alzheimer's patients and their loved ones," Missling says. "My grandmother and grandfather were affected by Alzheimer's. It is incredibly disheartening and sad to see the people you love slowly fade away, losing their personality and dignity as they are reduced to childlike behavior."

Under Missling's leadership, the company's frontrunner Alzheimer's drug candidates — ANAVEX 2-73 and ANAVEX PLUS are currently being evaluated in a Phase 2a clinical trial. Before his arrival, the advancement of ANAVEX 2-73 had stalled due to a lack of funding, and the synergies between the drugs combined to make ANAVEX PLUS had not yet been confirmed in a second model. With funding in place, enrollment for the Phase 2a trial of ANAVEX 2-73 and ANAVEX PLUS began in January 2015. Dosing

of the first patient was reported later that month. Preliminary data results for Phase 2a are expected around Q3 2015.

While progress in advancing Anavex's drug candidates has been apparent during Missling's short time with the company, there have been challenges along the way.

"All Alzheimer's drug trials have failed in the last 10 years," Missling says. "That makes it challenging for us to attract investors, especially as a small company. The recent clinical disappointments for Alzheimer's have focused on removing abeta plaques in the brain, which may be too simplistic and too far downstream an approach to be effective. Instead, we took a different approach: Target the potential cause of the disease, further upstream. Our view is that Alzheimer's could be caused by chronic cell stress, which, in turn, could trigger protein misfolding in the brain. Anavex's drug candidates are not targeting the downstream protein aggregations itself. Rather, the drug candidates take a further upstream neuroprotective strategy that may help the brain to either prevent or remove the protein misfolding in the distressed cells."

Anavex now boasts a team of four, supported by three directors and a 10-member scientific advisory board.

"Before I came to the company, Anavex had completed a Phase 1 clinical study for ANAVEX 2-73, but not much progress was made in the following two years, and funding remained scarce in the marketplace," he says. "When I arrived, I knew I had to raise a significant amount of money for the company to survive for at least a year. I had the top goals of raising funds and the implementation of a clinical trial, while demonstrating accountability to shareholders regarding the direction of the company."

Since he has been CEO, Anavex has obtained key funding commitments, notably $10 million in March 2014 from several institutional and accredited investors. With approximately $6.3 million remaining in its treasury, Anavex is funded through the current Phase 2a clinical trial.

"During my early days at the company, I spent a great deal of time building a target list of investors and institutional funds. I used my prior relationships in the investment community, and I reached out to new investors, targeting those that may be more inclined to invest at the Phase 2 stage in the clinical process. When making investor presentations, I focused more on the science as the driving force to present the merits of the drug, and I enlisted data from a study evaluating ANAVEX 2-73 in a computer simulation

model of Alzheimer's disease. The simulation of the drug candidate's effect brought gravitas to the science for the investors."

When trying to raise funds from the life science investor community, Missling says he had to educate prospective investors about Alzheimer's market size and implications, as very few financiers had prior experience in investing in trial drugs for this indication.

"In presentations, it was important to communicate that the Alzheimer's indication is the biggest and fastest-growing market (now affecting approximately 5.3 million Americans), and the baby boomer generation is coming to an age that will increase this market growth. At the same time, the healthcare system today is very effective in extending people's lives, thus increasing the chances of getting Alzheimer's since it is so highly correlated with aging. Once I showed these co-relations, it was easier to demonstrate an increasing need for a new generation of Alzheimer's drugs that address the cause and not just the symptoms."

Today, Anavex has no debt, and the company's burn rate is relatively moderate. "We are focused entirely on the trial," Missling told attendees of a recent investment conference, "With our current cash position, we can move forward for almost two years without any additional funding."

With sufficient funding to advance Anavex's lead Alzheimer's drug candidates to a Phase 2a trial, Missling has also been able to attract top talent to the company. "We were able to bring Dr. Tasos Zografidis to the Anavex team as VP of clinical operations. He has more than 25 years of experience in the pharmaceutical and healthcare industry. Dr. Zografidis manages Anavex's clinical programs and has extensive expertise in applying population pharmacokinetics, which analyzes variability in drug concentrations between patients and provides additional safety details often requested by regulatory authorities. His expertise has been invaluable to us during our current Phase 2a trial, as well as for the intended next phase."

Anavex's promising science also has helped attract top industry talent to its scientific advisory board, such as key Alzheimer's opinion leaders Dr. Jeffrey Cummings of the Cleveland Clinic and Dr. Paul Aisen of the University of California, San Diego School of Medicine's Department of Neurosciences. The scientific advisory board also includes doctors from the industry, like Michael Gold, who codeveloped one of the four approved drugs in Alzheimer's during his tenure with J&J; John Harrison, an expert in cognitive trials; and Ottavio Arancio, a specialist in amyloid-beta from Columbia University. "We have brought together an array of Alzheimer's experts with specialization in different parts of the indication. Each person brings a unique area of knowledge and research, yet there is a common ground to collaborate. I will continue to add to the board to further build Anavex's expertise, reputation, and focus on finding a potential cure for Alzheimer's."

## TRANSLATING COMPLEX BIOLOGY

Discussing the scientific-business model, Missling says that ANAVEX 2-73 and ANAVEX PLUS might possibly address both the root cause of Alzheimer's as well as its symptoms.

ANAVEX PLUS, in particular, represents a great opportunity for the company. It's a combination of ANAVEX 2-73 and donepezil, the generic version of Aricept and currently the world's best-selling Alzheimer's drug. When combined, the two drugs have been shown to reverse memory loss and neuroprotection up to 80 percent more than when they are administered individually. Furthermore, a patent application filed for the combination drug would, if granted, provide protection until 2033.

"My biggest challenge as CEO is to inform the shareholders and the life sciences community that the data we have at hand is very promising, but needs to be further proven with human clinical trials. I need to explain the various hypotheses of the underlying disease mechanism, which then needs to be correlated with our technology and how it potentially addresses the disease origination."

Missling notes that a complex biology underlies the challenges of advancing Alzheimer's drugs to the clinical stage. "Other indications such as oncology and infectious diseases can use animal and biomarker predictive models to closely correlate the effect of the drug in humans. In contrast, Alzheimer's is very complicated. The brain is one of the most complex areas of the body, and we have not learned enough about it to understand what to do in order to advance a drug in the right direction. We believe Anavex is on the right path, though, but we still have to improve our success rates."

## FUTURE TRENDS IN ALZHEIMER'S FINANCING

While Anavex is comfortably financed for Phase 2a, its CEO tracks funding trends within the Alzheimer's indication. For example, the Dementia Discovery Fund is a newly created $100 million global fund to assist small biotechs and entrepreneurial ventures in their efforts to find a treatment or cure for Alzheimer's. It is supported by the British government, the charity Alzheimer's Research UK, Johnson and Johnson, Eli Lilly & Co, Pfizer, Biogen Idec, and GSK. "This fund is great news; however, funding for Alzheimer's is still much lower compared to cancer funding," Missling says.

He also notes the scarcity of Alzheimer's research monies as compared to the growing costs of caring for patients with the disease. For example, for every $27,000 Medicare and Medicaid spends on caring for individuals with Alzheimer's, the NIH spends only $100 on Alzheimer's research. "Caretaking costs can put Medicare in a precarious place financially, even possibly bankrupting it," Missling says. "Medicare's expenditures will triple from currently $300 billion up to $1.5 trillion by 2050 if no cure is found."

When the complete results for the Phase 2a trial are announced, potentially another chapter in Anavex's story will be told. Meeting an unmet medical need with a new drug lends itself to profits for investors, cost savings to caregivers and the healthcare system, and relief for patients. L

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# 7 Steps For Boosting Your Influence

TERESA SHAFFER

Today's organizations are filled with great complexity, undergo rapid change, and have a wide array of workplace cultures and team dynamics. Leaders are expected to influence many people in order to create effective change and deliver better results, all while inspiring and empowering others. Influential leaders are those who can garner help from enough people throughout the organization to achieve or exceed shared goals.

Here are seven steps you can take to elevate your influence:

1. **BUILD AUTHENTIC RELATIONSHIPS.** The ability to build strong relationships with peers, employees, stakeholders, and others is vital to increasing your influence. Step into other people's shoes to understand their talents, goals, and pressures by asking great questions and listening deeply. Foster meaningful relationships by genuinely caring about others, adding value to their lives, and helping them succeed.

2. **DEMONSTRATE IMPECCABLE CHARACTER.** Strong leaders have strong character and can inspire trust. Influence begins with trust, and it affects a leader's influence enormously. Trust begins with building credibility. Define your values such as courage, honesty, loyalty, and integrity, and align your behaviors with these values. Demonstrate respect. Keep commitments.

3. **INSPIRE OTHERS TO WANT TO DO THE WORK.** One way to influence a person is to link what you want with reasons and interests that matter to the other person and explain the win for them personally and for the business. Always show your gratitude for people's help, acknowledge contributions, and celebrate victories.

Teresa Shaffer, CEC, CPC, RN worked in healthcare and built an award-winning corporate career. She specializes in executive coaching for leaders in organizations. For more information, visit www.shafferexecutivecoaching.com.

4. **PLAN AN INFLUENCE CAMPAIGN.** Who are the key people involved in the decision? How much does each person support the idea? Do enough people with enough power support the idea? Success depends on assessing the situation in advance, mapping out the terrain, assembling the right people, and setting specific and measurable goals.

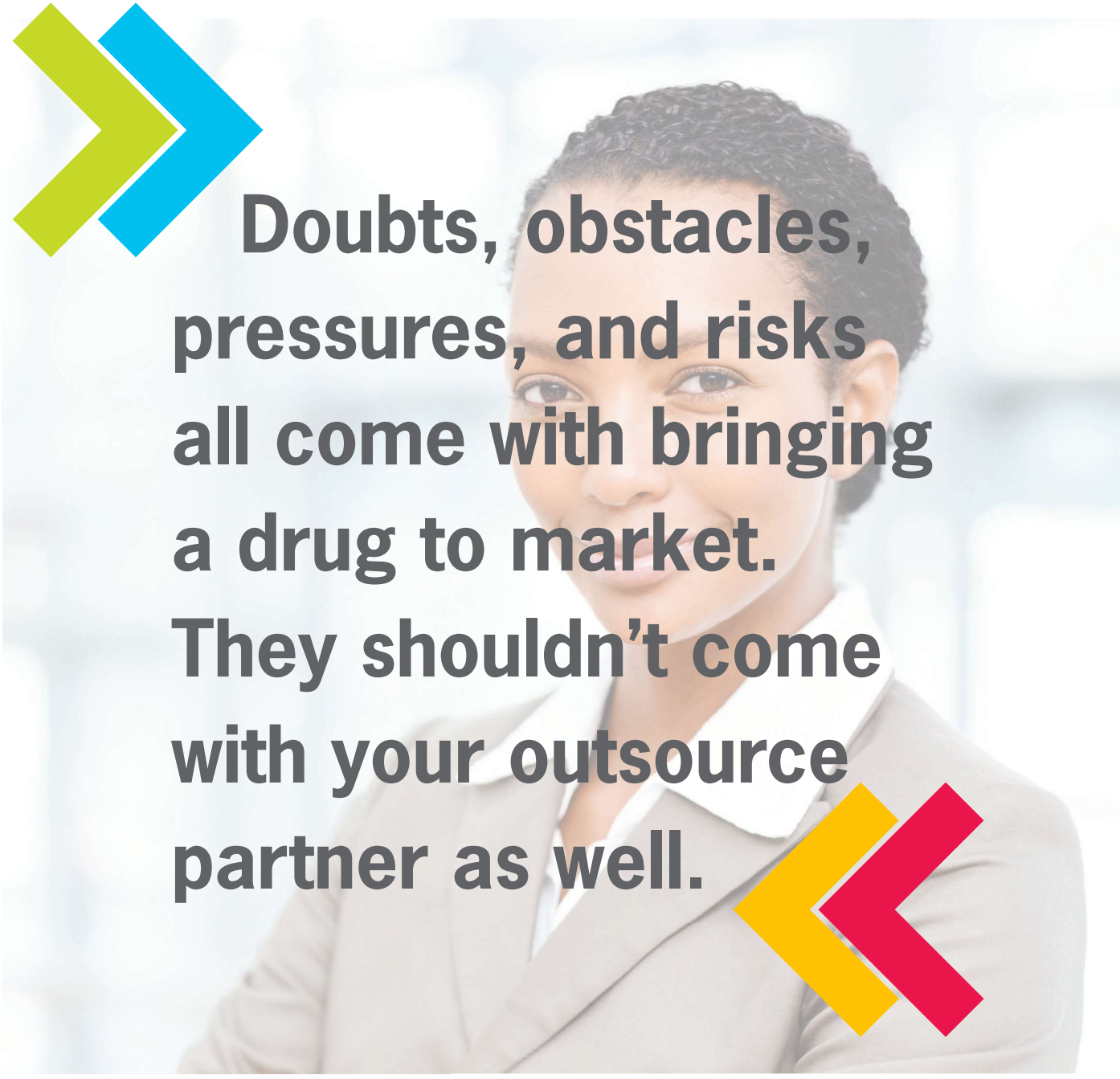
5. **FOSTER COLLABORATION.** Organizations are becoming less bureaucratic and more collaborative. Influential leaders build coalitions that have a variety of expertise, share responsibility, and decide on important matters collectively. This kind of collaboration empowers the group and benefits individuals and the organization.

6. **CLEARLY ASK FOR WHAT YOU WANT.** Make the case, give reasons, and ideally communicate a mutual desired outcome; this helps motivate people to act. Don't assume that those listening to you heard correctly; verify that you're all on the same page through back-and-forth dialogue. Effective leaders communicate openly and frequently.

7. **EXPERIMENT WITH DIFFERENT APPROACHES.** You might succeed, or you might fail when attempting to influence another person. If you fail, you can consider adjusting your style or trying a different approach. When it comes to influence, there are no guarantees. Learn to do it better next time, and keep moving forward.

The most influential leaders collaborate, connect, empower, persuade, and help others succeed. They create win-win solutions, drive better business results, and strengthen the organization.

How might you put one of these influence steps into practice today? L

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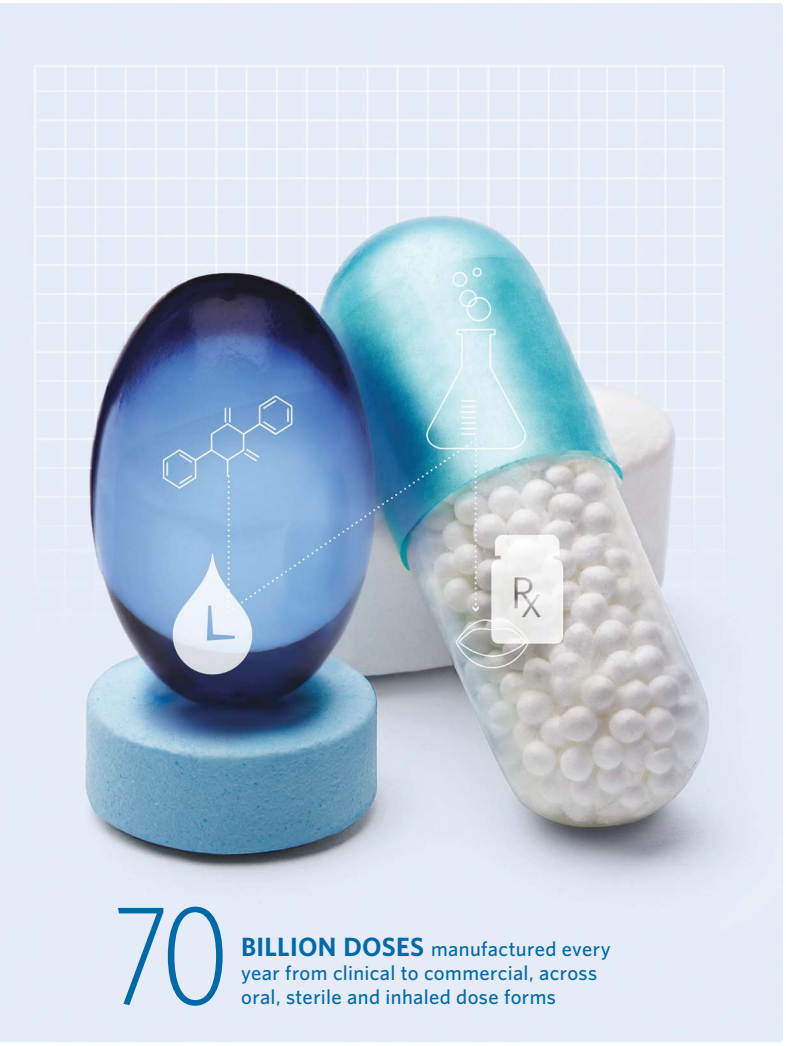


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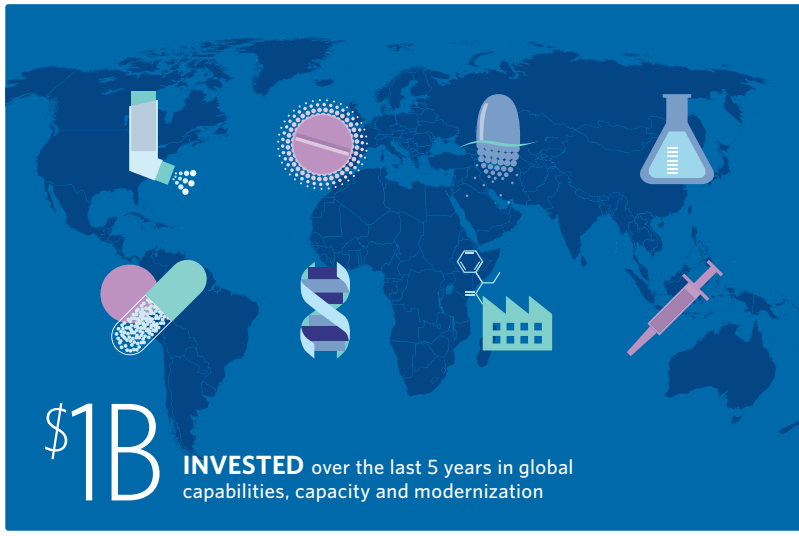

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