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MAY 2015

Purdue Pharma: Balancing Social Responsibility & Prescription Volume

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MAY 2015

Purdue Pharma: Balancing Social Responsibility & Prescription Volume

"Getting the company to buy into the future vision happened quickly, but the way to getting there is not a smooth road." p. 16

MARK TIMNEY
President and CEO, Purdue Pharma

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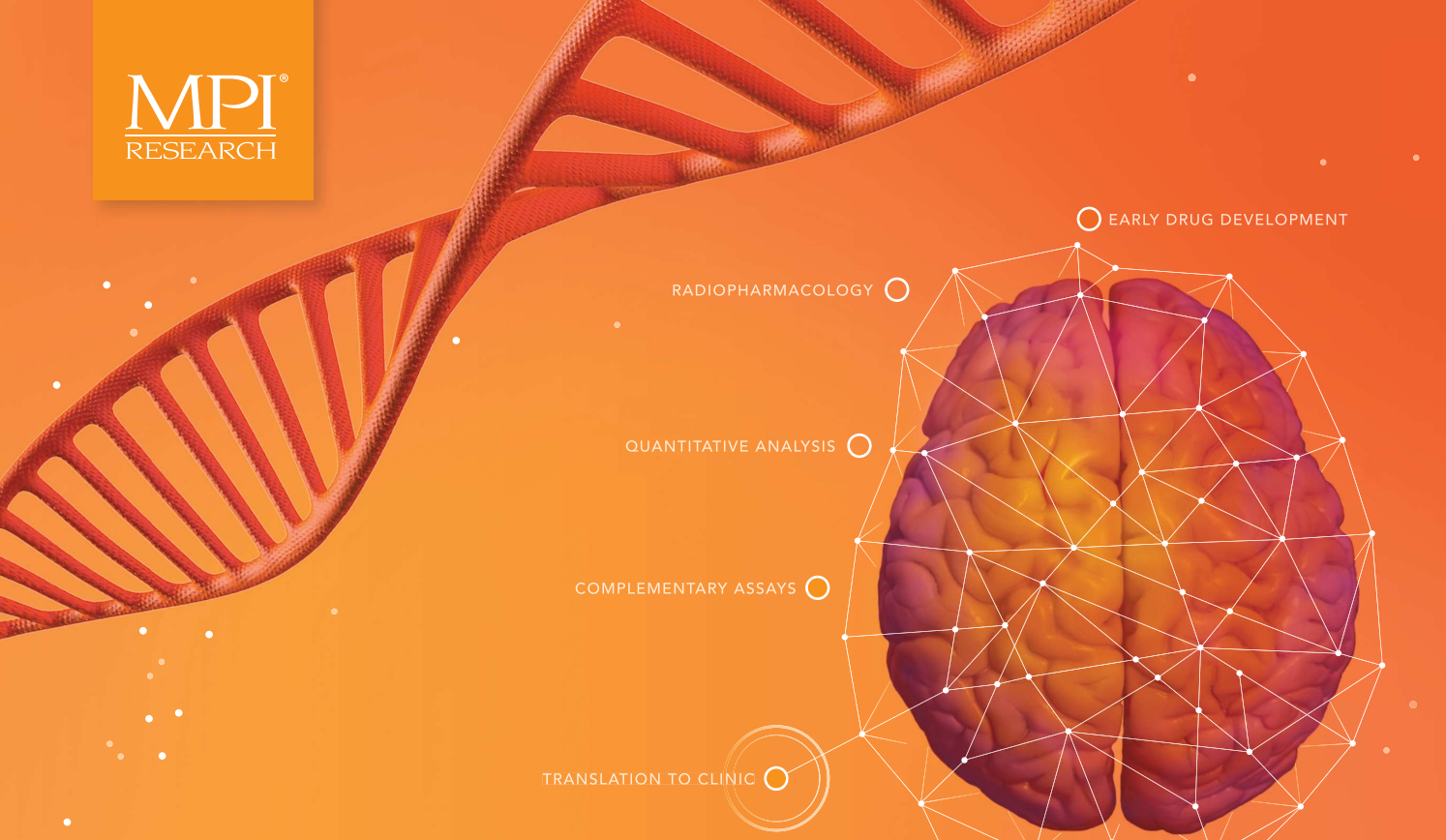

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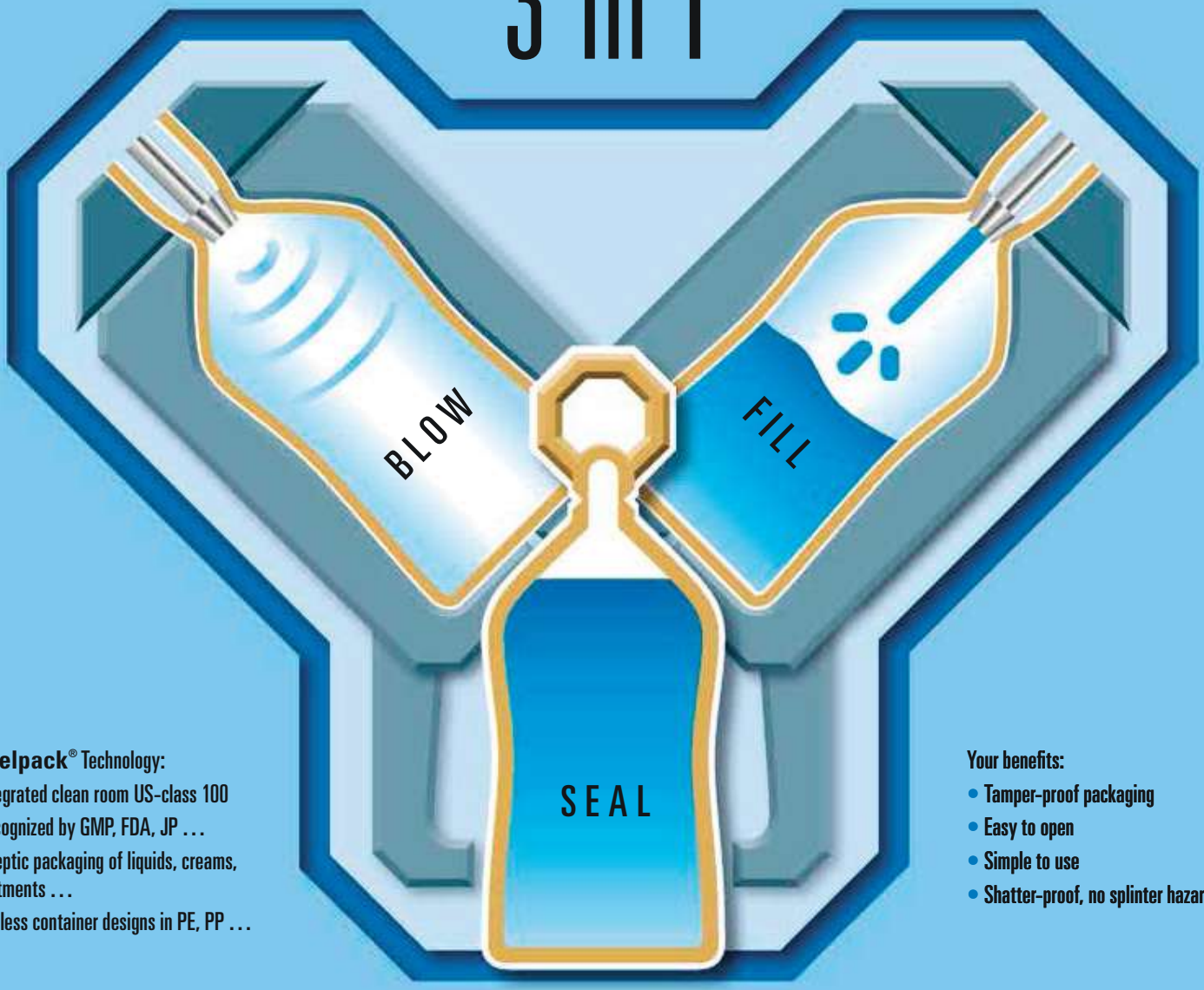

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CONTENTS

Welcome to

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MAY 2015 VOL. 7 NO. 5

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Features:

24
So You Want To Start Your Own Biotech?
The president and CEO of a small biotech shares his struggles and lessons learned.

30
The Price Wars From All Sides
Will innovative new drugs now be rejected or reduced to the level of commodities in the United States?

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It's Time For PhRMA To Get Better At Managing The Message

ROB WRIGHT Chief Editor

Last month, the Pharmaceutical Research and Manufacturers of America (PhRMA) held its 2015 annual meeting in Washington, D.C. In years previous, the event served as a two-day public conference scheduled around PhRMA's annual board of directors meetings and encompassed panels and presentations. Last year's speakers included a U.S. Senator, a Nobel laureate, and the former commissioner of the FDA. However, perhaps one of the most important presentations last year came from a patient — Suleika Jaouad. An Emmy Award-winning *New York Times* columnist, Jaouad shared her experience of being diagnosed and treated for cancer. Although inspirational, her most important message came when she spoke directly to Celgene CEO, Bob Hugin, stating, "I have no words to describe how thankful I am to Celgene," crediting the company's chemotherapy drug, azacitidine, for keeping her alive.

Unfortunately, neither public messaging nor public attendance played a role in the 2015 annual meeting. While I applaud PhRMA's willingness to embrace change, I question the timing as to why the organization moved to more of a "closed door" meeting this year. PhRMA informed us they just aren't doing a public meeting this year, but are open to considering them in the future.

Though the thinking may be a strategic circling of the wagons against the barrage of recent drug pricing attacks, the shift by PhRMA may create a negative perception, providing an opportunity to be exploited by the health insurance industry.

America's Health Insurance Plans (AHIP) is a national trade association consisting of 230 companies. This means that AHIP has more than four times the membership of PhRMA and thus, a much larger wallet with which to wield influence over public opinion. And there are plenty of examples of how the pharma industry is losing the battle for public opinion.

For instance, in March 2015, Express Scripts, a pharmacy benefit management (PBM) company, released its 87-page 2014 drug trend report, in which it stated that overall drug spend increased by 13.1 percent. Later that month, when the *Wall Street Journal* published the announcement of UnitedHealth Group's acquisition of Catamaran, the article mostly focused on how the deal was aimed at curbing rising drug costs. Citing the Express Scripts report, the *WSJ* article noted escalating drug prices as being "the biggest annual increase in more than a decade."

In the report I found an interesting contradiction on page five — "Absent more fair drug pricing, payers will face half a trillion dollars in prescription drug costs as soon as 2020." Perhaps it is time PhRMA takes a page out of the playbook of George Paz, CEO of Express Scripts. In a 2014 letter to Express Script shareholders he writes, "In this environment, the choice is clear: act or be acted upon." Isn't it time PhRMA stops letting health insurance Goliaths get away with continuing to successfully play the role of David with the American public? Instead of PhRMA closing its doors to this year's annual meeting, maybe it is time to think about swinging them wide open and take charge of managing the message. If PhRMA wants to win in the court of public opinion, the message has to focus on drug price and value, not jobs and innovation.

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Q What regulatory requirement should be streamlined?

A ONE OF THE MOST NEEDED HARMONIZATION TOPICS would be post-approval change. Right now a post-approval change can take up to four years before it is fully accepted by global regulators, which not only adds to the burden of the drug manufacturers, but also increases the opportunity for errors. These errors or failures can be manifold. For example, depending on the post-approval status, a manufacturer might produce the same product using different process technologies. One process could use a new update that has been approved by one regulatory agency, while another process requires old technologies, since another agency has not approved the updated technology yet. This resource and financial burden also may result in the hesitancy to modernize processes or facilities, resulting in aging facilities, which again have been recognized as a culprit for drug shortages.

MAIK JORNITZ
Maik Jornitz is COO of G-CON Manufacturing and founder of BioProcess Resources. He has more than 25 years of experience.

Q Has a medicine's efficacy ever been demonstrated using a method other than a double-blind randomized design?

A YES, BUT IT'S USUALLY RESTRICTED to rare or life-threatening conditions. A recent example is lynparza for ovarian cancer, approved in December 2014. Here's an excerpt from the FDA medical review: "The recommendation for approval is based on the single, open-label, nonrandomized trial in which olaparib demonstrated a robust overall response rate with a clinically meaningful duration of response in patients with deleterious or suspected deleterious germline BRCA mutation (gBRCAm)-associated ovarian cancer who had received three or more prior lines of chemotherapy." This trial enrolled 193 patients with gBRCAm-associated ovarian cancer, including 137 patients who received three or more lines of prior chemotherapy and with measurable disease who were treated at a dose of 400 mg PO BID. The overall response rate in the patients with measurable disease was 34 percent with a median duration of response of 7.9 months.

DR. MITCHELL KATZ
Dr. Mitchell Katz has 30 years' experience in the pharmaceutical and biotechnology industries, including preclinical research, pharmaceutical operations, and regulatory affairs. He is the Head of Medical Research and Drug Safety Operations at Purdue Pharma L.P.

Q What is the best leadership advice you ever received?

A IT WAS TO "EMBRACE DIVERSITY." I learned this sage piece of advice from my grandmother who traveled from Scotland on her own across the Atlantic at a young age to make her way in the land of opportunity in the U.S. She saw firsthand the strength that America had was because of, not in spite of, its melting pot of cultures. I'm privileged to serve as the CEO of an organization that promotes the benefits of gender diversity, and I practice this advice daily. Studies show that every team and every company gains from diversity. No one person has all of the answers. We come at issues from different points of view based on our personal tapestry of experiences, and we solve problems using varying methodologies.

LAURIE COOKE
Laurie Cooke, BS, RPh, PGDip, CAE, is the CEO of the Healthcare Businesswomen's Association (HBA), a global nonprofit professional association.

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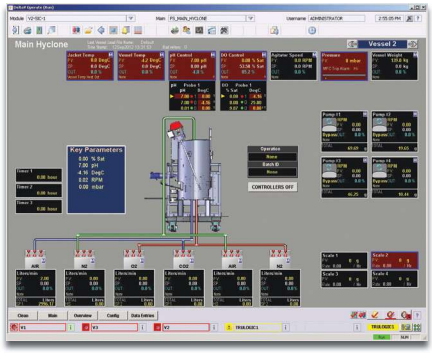

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Patent Reform Pits Life Sciences Against High-Tech And Hedge Funds

JOHN McMANUS The McManus Group

Shivers went down the spine of many biotech executives when Kyle Bass' hedge fund, Hayman Capital Management, announced it would exploit a relatively new provision in patent law that allows any person (not just a generic competitor or related party) to challenge and invalidate patents at the U.S. Patent & Trademark Office (USPTO).

Acorda Therapeutics' stock fell about 10 percent in one day with the news that the patent for Ampyra, the company's treatment for MS, was being challenged by Hayman Capital under the new "*inter partes* review" (IPR) process at the Patent Trial & Appeal Board. Bass had apparently shorted the stock in advance and made millions overnight.

IPR was enacted as part of the America Invents Act of 2011, in large part at the insistence of the high-tech industry (Google, Apple, Microsoft, etc.) which was being plagued by patent trolls — shell companies with no manufacturing or supply capacity that simply obtain patents in order to extract settlement agreements or launch infringement lawsuits and extract licensing fees. Sometimes the patent claims in question have been drawn improperly broadly or are not actually infringed, but it may require several million dollars and years to litigate the matter through the federal courts including appeals. IPR is designed as a faster, less costly alternative to litigation.

The high-tech industry's business model is markedly different from the life sciences industry. Unlike the 10 to 14 years it takes to bring a drug from discovery (when only a handful of patents are filed) to market, high-tech products (that rely on hundreds or even thousands of patents per product) are brought to market in relatively short order. Patents for these products become obsolete in a couple of years and are seen as nuisances, as the next generation of products are produced and marketed. In contrast, a novel biopharmaceutical is protected by only a few patents, which are reported and published by the FDA's *Orange Book;* a process that essentially announces, "Look at me, I am very important!"

Thus, IPR was intended to provide a speedier and less-expensive alternative to typical court proceedings. The IPR process also requires a lower burden to prove invalidity, utilizing a "preponderance of the evidence" standard (i.e., 51 percent) with no presumption of validity, whereas federal courts require "clear and convincing evidence."

Moreover, where federal court proceedings can cost millions, IPR may cost only a few hundred thousand dollars. It was meant to require that patents have the narrowest application that do not conflict with prior art (knowledge that already exists). Due to advantages in proceedings, the "kill rate" (or invalidation rate) of patents at the IPR is nearly 80 percent compared to 45 percent in court.

"Individuals should not be permitted to hamper innovation by extorting America's inventors."

Hedge funds and others clearly have taken notice — and taken aim. The IPR process permits *any* party to bring the challenge, not just competitors. While some hedge funds adopt Hayman Capital's approach of shorting the stock, others are demanding extortion-like cash settlements.

CAN LIFE SCIENCES FIND LEGISLATIVE RELIEF?

The drug industry now has turned to Congress for legislative relief but finds a generally inhospitable environment. Last Congress, the House of Representatives passed Judiciary Chairman Bob Goodlatte's (R-VA) high-tech-friendly patent reform legislation with 345 votes. He has reintroduced the identical bill — The Innovation Act — feeling little need to change the bill.

But the life sciences industry and many others, including universities, are now mobilizing. On April 14 the Biotechnology Industry Organization (BIO) testified at the House Judiciary Committee, stating: "IPR is undermining the value and predictability of patent rights and wreaking havoc on legitimate, investment-backed expectations of patent holders. ... The biotechnology industry is particularly vulnerable to [stock price] manipulation, because the vast majority of our industry consists of small companies that tend to derive most of their revenue from one or two products on the market, and — unlike cellphones or computers — have just a handful of very valuable patents protecting those products. The mere filing of an IPR can have a significant impact on the stock prices of such companies, as well as their ability to continue to raise the investment needed to develop future treatments for patients in need."

Bob Armitage, a patent expert with long experience in the life sciences industry, testified that changes to the IPR system are in order so that the proceeding "could no longer be perceived as legal nectar for investment bees looking for their next sting."

BIO also argued that the patent troll concern may be overstated. A 2013 Government Accountability Office report noted that alleged patent trolls file less than 20 percent of litigation cases, while traditional businesses file 68 percent of patent litigation.

Moreover, the patent landscape has changed since enactment of the America Invents Act. The Supreme Court decided five patent cases that: **1)** make it easier to defeat patents and have fee-shifting awarded in appropriate cases; **2)** narrow the scope of patentability; and **3)** disincentivize meritless claims. Indeed, patent suits have dropped 18 percent from 2013 to 2104 (5,008 vs. 6,083, respectively). Judges are now granting 80 percent of all motions to stay patent litigation if the patent is also involved in a parallel IPR or "covered business method" proceeding.

Yet much of Goodlatte's legislation would make it more difficult and costly to defend patents and create more uncertainty for innovators. For example:

- new requirements under which initial complaints in patent lawsuits would be required to provide increased detailed information or be deemed insufficient and subject to motions to dismiss

- mandatory stays of discovery pending patent claim construction, forcing delays as much as a year or more in typical litigation.

However, there is one positive in the legislation for the life sciences industry. The bill repeals the broadest reasonable interpretation (BRI) provision — the pre-patent review standard designed to narrow claims so they do not conflict with prior inventions. But the life sciences industry, the American Bar Association Intellectual Property Law section, the American Intellectual Property Law Association, and the Intellectual Property Owners all argue that the bill should adopt the same rules applied by federal courts, i.e., presumption of validity and "clear and convincing evidence." (Senator Christopher Coons [D-DE] recently introduced legislation making those reforms.)

Republicans are also enamored with the "loser pays" fee-shifting provisions in Chairman Goodlatte's bill because they believe it will discourage frivolous lawsuits from patent trolls. That provision is seen as a substantial advance in tort reform. While it unites the high-tech industry and many large pharmaceutical companies, it has sparked opposition of the trial bar, universities, and small biotech companies, making for messy politics.

PROSPECT FOR FUTURE ACTION

Lobbying by all affected parties has been intense, since the House Judiciary Committee will soon mark up its legislation, and a new legislative package also is expected in the Senate led by Majority Whip John Cornyn and future Democratic leader Chuck Schumer — an odd but very powerful duo. But the outrageous actions by certain hedge funds could spark the similar interest that initiated action on behalf of the high-tech business community with respect to patent trolls: individuals should not be permitted to hamper innovation by extorting America's inventors. What hangs in the balance? Increased speed of Google's search engine ... and fundamental harm to the most innovative and rewarding medical development system ever seen. 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.

AvidBiotics

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

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

AvidBiotics is in early development of "precision antibacterials" from its basic technology platform based on R-type bacteriocins, proteins secreted by Pseudomonas bacteria that kill other bacteria with extremely potent "single-hit kinetics" — it only takes one bacteriocin molecule to kill a bacterium. The company has engineered the bacteriocins to target specific bacterial strains that remain or have become problematic. It has two lines of engineered bacteriocins: "Avidocin" proteins, against infectious bacteria in humans; and "Purocin" proteins, versus contaminating bacteria in food and animals. A third technology line, "Micacide" proteins, uses a different targeting mechanism to draw the immune system to attack virus-infected cells and cancers.

WHAT'S AT STAKE

One word, *precision,* promises many benefits. For years, the standard goal for all new antibiotics was a broad spectrum of activity — the ability to kill multiple species of "bad bugs" with a single drug. A broad spectrum gives doctors the freedom to prescribe a drug with the near certainty of scoring a hit on whatever bacterial strain may have invaded the gut, the skin, the ear, and so on. But the shotgun approach also encourages overprescribing and widespread misprescribing of such antibiotics for almost any infection, driving antibiotic resistance. Meanwhile, many *good* bugs die a wasteful and damaging death, robbing patients of their protection. Drugs that can target individual species and strains will avoid all of that.

AvidBiotics believes it has such a remarkable arsenal in the making. Its engineered bacteriocins appear to strike with extraordinary precision, against gram-positive and gram-negative bacteria alike. David Martin, M.D., CEO, cofounded the company with James Knighton, president, in 2004, and Jeffery F. Miller, Ph.D., following an interest in bacteriocins as a potential new approach to drug-resistant bacterial strains. Rather than merely pursuing new mechanisms and compounds that would have the same broad-spectrum effects as the older ones, they chose precise targeting of single bacteria types as the possible next paradigm in antibiotics. "We like to call our approach 'precision drugs for bad bugs,' rather than new drugs for bad bugs," Martin says.

"With a precision agent, you can kill a particular strain or species of a bug, but you don't put any selective pressure on other bacteria to retain or gain antibiotic resistance. You can avoid the unintended collateral damage to the gut microbiota, vaginal microbiota or skin microbiota. In particular, the gut microbiota has an enormous impact on the immune system as well as the hormonal, CNS, cardiovascular, and other vital systems in the body."

With their narrow specificity, precision antibiotics should lack the wide-ranging side effects of conventional antibiotics — so they could be considered for prophylactic use, to *prevent* rather than cure infections. Though the pharma industry is traditionally averse to prophylaxis, physician demand for better antibiotic solutions and payer demand for the potential cost-savings of prevention could press the industry to alter its perspective.

AvidBiotics has another fascinating technology in its Micacide proteins, which single out cells emitting signals of stress from viral infection or cancer. Although the antiviral angle is impressive, the oncology application is especially fascinating now, amidst the rise of cancer immunotherapy. Martin believes Micacide proteins may be another major key to unlocking the immune system to fight cancer, alongside the checkpoint inhibitors and other contenders for immunotherapy combinations.

DAVID W. MARTIN, M.D.
CEO

Vital Statistics

17
Employees

Headquarters
South San Francisco, CA

Finances

Raised
$31M
Various sources – founding management, individual investors, NIH grants, corporate collaborations and investments, equity and R&D support.

Research partnership funding

DuPont – Food Safety R&D; Cubist/Merck – Microbiome and targeted antibacterials; Zoetis – Animal Health R&D.

Latest Updates

March 24, 2015:
Publication (mBio) describes animal efficacy of bactericidal (Avidocin) protein very specific for Clostridium difficile.

February 2014:
MICA-based bispecific (Micacide) protein demonstrated efficacy in xenografted human solid tumors in mice.

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Building A Successful CMO/CRO Partnership: What's Important To Emerging Pharma And Emerging Biotech?

More than ever, pharmaceutical and biotechnology companies are considering CROs and CMOs as partners in collaboration to achieve long-term development goals.

NIGEL WALKER
Managing Director
at That's Nice

"Looking at the impact of company size on outsourcing relationships, there are strategic partnership opportunities for businesses and outsourcing companies of all sizes."

The Nice Insight 2015 industry survey of emerging pharma buyer groups showed how these companies today are choosing and evaluating strategic partners and the provider qualities that are most important to them. For the purposes of the survey, a strategic partnership is defined as a long-term commitment between two organizations to achieve specific business objectives by maximizing the effectiveness of each participant's resources. The survey indicates that nearly three-quarters (73 percent) of the emerging pharma companies surveyed are interested or very interested in becoming involved in a strategic partnership with a CRO or CMO in the next 12 to 18 months.

The most important considerations made by emerging pharma companies when choosing an outsourcing partner are the provider's financial stability and history of success (both 31 percent), followed closely by their operational, methodological, and therapeutic experience (28 percent). Also important are adaptability (27 percent) and range of service offerings (23 percent). Among the lesser important attributes influencing their choice are the use of contractors in emerging markets to save costs (17 percent) and the size and structure of the outsourcing organization (15 percent).

When emerging pharma buyers evaluate CROs or CMOs, the three most important qualities that influence their assessment are a provider's industry reputation for doing quality work, followed closely by its responsiveness, transparency, and good communication, and by understanding the customer's requirement. Cultural fit is considered least important. In terms of the methods used to assess a partner, unbiased peer reviews are extremely important, especially when trying to determine which outsourcing companies will work well with a company like theirs.

Looking back, comparing selection methods of emerging pharma and emerging biotech companies in the 2014 Nice Insight survey, emerging pharma companies placed considerable importance on referrals from colleagues (71 percent), followed by industry research (66 percent) and consultants (65 percent). Emerging biotechs showed less reliance on referrals (29 percent) and more on industry research and consultants (52 percent each). Emerging biotechs sought out CROs at trade shows and events (38 percent); however, more than half of emerging biotech companies

attended trade shows to identify CMOs.

Coming back to 2015, in terms of work style preferences, emerging pharma companies rank operating procedures that are established collaboratively and long-term commitment as the most important factors when they evaluate a CRO or CMO as a strategic partner. The attribute of customized protocols is another important factor.

The biggest sources of dissatisfaction for emerging pharma when working with CROs and CMOs are unexpected charges, the timeliness of resolving issues, and product quality, with nearly one-third of companies naming each of these concerns.

Not surprisingly, the most important measure of a CRO's or CMO's project performance is the quality and accuracy of its work (50 percent). Other important performance-related factors include results of safety and compliance audits (44 percent) and technical expertise (44 percent), followed closely by cost-effectiveness (42 percent) and on-time delivery (41 percent). Least important of the listed performance factors is billing practices (23 percent).

Looking at the impact of company size on outsourcing relationships, there are strategic partnership opportunities for businesses and outsourcing companies of all sizes. However, smaller companies and emerging companies who contract with big CROs worry that their projects will receive significantly less attention than the CRO's strategic partnerships. Smaller CROs are concerned there won't be a place for them in the industry, since their offering is narrower, and they cannot provide support services across the entire development cycle.

Downplaying these concerns, Nice Insight data shows that CROs with a solid customer perception score from Big Pharma or Big Biotech have similarly strong scores across other smaller buyer groups. In fact, the larger the percentage of businesses that have worked with the outsourcing company, the higher the customer perception score across all company sizes. The 2014 research showed that for Big Pharma, the lowest percentage of projects went to tactical providers* (23 percent), and nearly half (47 percent) went to preferred providers** rather than strategic partnerships*** (30 percent). Big Biotechs allocated approximately one third of their business to each type of relationship. Biotechs also showed the strongest interest in forming strategic partnerships.

The 2014 research also revealed that emerging pharma and emerging biotech companies allocated the smallest percentage of projects to strategic partnerships (27 percent). It also revealed, however, similar interest levels to Big Pharma in forming strategic partnerships — 43 percent were interested, compared to 46 percent of Big Pharma companies. Although emerging pharma and emerging biotechs' allocation of projects to strategic partnerships was smaller than that of their larger counterparts (Big Pharma and Biotech), and perhaps there was some apprehension with respect to forming strategic partnerships, there were significant advantages for emerging pharma and emerging biotech companies in forming these partnerships, especially with global CROs. Partnering with a CRO enabled these businesses to quickly and easily expand their expertise and gain access to the latest equipment, methodology, and technology.

DEFINITIONS

***TACTICAL SERVICE PROVIDER**
The primary focus of these relationships is to meet the particular development needs of individual drugs as they move through the development continuum. Tactical service providers offer operational cost benefits, but are not designed to drive competitive advantage or shareholder value.

****PREFERRED PROVIDER**
A group of carefully selected providers that have been thoroughly evaluated through due diligence. These relationships frequently offer shorter setup times and higher quality deliverables because the CMOs are thoroughly versed in the specifications of the sponsor.

*****STRATEGIC PARTNER**
A long-term, win-win commitment between two organizations for the purpose of achieving specific business objectives by maximizing the effectiveness of each participant's resources.

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Emerging Pharma and Emerging Biotech Value Different Traits in CROs, *Life Science Leader*, August 2014

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, at Nice Insight by sending an email to nigel@thatsnice.com.

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2014-2015 report includes responses from 2,303 participants. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top ~125 CMOs and ~75 CROs servicing the drug development cycle. Five levels of awareness, from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

PURDUE PHARMA

from

PRIVATE FRANCHISE

to

OPEN BUSINESS

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

MARK TIMNEY
President and CEO, Purdue Pharma

In some ways, it is easy to see Purdue and its singular pain-med focus as a model preserved from the time I began covering the industry in the mid-1980s. The typical pharma company back then had a franchise, sometimes a virtual monopoly, in a given area, and the industry overall was more collegial than competitive.

As now with Purdue and others, some of those companies specialized in controversial areas that exposed them to legal or regulatory difficulties, which they accepted and adapted to as a necessary part of doing business. Most of them no longer exist, having vanished into the various industry giants formed by the mega-mergers of subsequent decades. Purdue persists, though.

But the company's persistence to this point does not mean it is immune to change. In fact, right now it stands on the cusp of a large-scale transformation that will turn the heretofore taciturn company into a model of transparency and simultaneously expand its franchise into new but not entirely unknown areas.

Purdue is actually one of the industry's pioneers and still preserves some of the old, pre-Big Pharma model as a midsize, franchise-driven company. At the same time, the traditionally opaque, family-owned company is coming out of its shell under the banner of corporate transparency as it begins to expand beyond its niche in the pain market into new areas within pain and outside it using its extended-release, abuse-deterrent technology as leverage. (See also, "Purdue's Path to the Pain Space," page 20.)

In many ways, Purdue represents a bridge in the industry between traditional pharma and smaller life sciences companies — a broad area with many companies fitting the title of specialty pharma. The company's relatively new president and CEO, Mark Timney, is also a bridge of sorts; originally from the U.K. and former head of Merck US, he has a global perspective on drug development, regulatory, and reimbursement issues that inform his strategic planning, but is also well-grounded in operations and tactical management.

Of course, the other side of the Purdue story is that it entered 2015 facing three major legal battles — in Kentucky, Chicago, and California — over its alleged role in increasing pain-med abuse. Thus, Timney discusses the challenge of balancing the company's social responsibility against the traditional pharma model of maximizing prescription volume.

Voice In The Light

Timney is a relatively fresh face at Purdue, having arrived to head the company in January 2014. He has declared a mission to turn the company's own face to the world, not only to see the outside more clearly, but also to be seen — transparently. The company remains family-owned, and founder Dr. Raymond Sackler still works at headquarters almost every day. (His brother and cofounder, Dr. Mortimer Sackler, died in 2010 at 93.) Yet Timney aims to operate Purdue on an open-corporation model, or transparency — maintaining a clear presence, voice, and dialog with payers, policymakers, and the public at large.

Timney also seems well prepared to apply his prior experience to steering Purdue through the toughening conditions set by payers and regulators in its largest market, the United States, now in the dawning era of outcomes-driven medicine. (Purdue is one of several Sackler-owned independent associated companies, which operate outside North America as Mundipharma.)

Timney was born and educated in the United Kingdom, where he subsequently worked as a representative for Rousell Uclaf, detailing to physicians, then for a number of companies in various countries, including Merck (MSD outside North America). "I have had the opportunity to work in diverse markets right across the world," he says, "so I've been involved in many different cultures."

Launching about 30 products in multiple therapeutic areas over the years, Timney says he gained valuable experience in guiding businesses through growth and rebuilding stages, which gave him a hunger for company management. "When the Purdue opportunity came up, it was close to an exact fit for me. I wanted to head an organization that was ready for change, ready to write the next chapter, even though it was unclear where that next chapter would lead."

He offers an example of how his background prepared him for market changes now just hitting the U.S. healthcare system — changes he has seen before in other places. "When I was a representative back in the U.K., it was already incredibly difficult to get access to GPs because the doctors' time was being reprioritized. It all changed from a treatment-oriented healthcare system to a preventive-oriented healthcare system."

Timney says a major turning point in the U.K. was the introduction of EMR (electronic medical record) systems more than 20 years ago. He saw the same effects of EMRs in other markets with single payers, including New Zealand, "probably the toughest payer environment in the world," and Australia, "another tough system that focuses a lot on health economics." But now, even in the United States' predominantly private-insurance system, he sees an

> *"Part of our strategy was a 'leaning' of the organization, a shrink-to-grow mentality."*
>
> **MARK TIMNEY**
> President and CEO, Purdue Pharma

almost identical transformation taking place.

"Obviously, as a single payer, once you know what you're going after, EMR makes it easier to measure and incentivize physician prescribing, and once you can incentivize, you can start to control behavior," Timney observes. "When I came into the United States, I saw a fragmented healthcare system, with powerful payers, and the government playing a certain role. Then I saw the EMR systems starting to take off and some of the quality metrics come into play, with various incentives being employed, and it seemed very similar to what I had seen among the government-run systems in other countries."

Real Pain, Real Pitfalls

An avid coach and player of international football, known in the United States as soccer, Timney says he has confronted the company's unique challenges, including all of the litigation, with almost athletic spirit. He says he pushes to get the best out of his team by "focusing on the positives, building on past successes, and planning how we will grow in the future." He credits past company management for making "difficult decisions" about dealing with the opioid-abuse issues while trying to ensure access for people with a genuine need for pain medication.

Even now, the company works in the midst of an ongoing debate about the appropriate use and inherent risks of opioids used to relieve specific types of pain and painful conditions. New drug MOAs (mechanisms of action) are emerging from discovery to challenge the time-honored place of opioids in some indications, such as shingles and neuropathic

PURDUE'S PATH *to the pain space*

Ever since its modern beginnings in 1952, when the brothers Mortimer and Raymond Sackler acquired tiny Purdue-Frederick, the company has tended to stay quiet and contained within a narrow space. Actually, it was a series of spaces, all ultimately leading to pain. One of the company's first sets of products included Pre-Mens, a treatment for premenstrual "tension," along with two vaginitis ointments.

The most outstanding fact of Purdue's founding was its immediate and apparently instinctive jump into niche franchise-building. Originally motivated by a desire to develop psychiatric drugs, the Sackler brothers started the company as a means to fund their R&D, and during the formative years of the company leapfrogged from one small group of related products to another – from gynecological to GI, to arthritis, to the ear, to antiseptics, and finally to pain.

Purdue's first million-dollar product, the laxative Senokot (senna), catapulted the company to a higher scale of international sales and infrastructure in the late 1960s, and its lucrative Betadine line added another rocket thrust in the same period. (In a close metaphor, Betadine was used to sanitize the Apollo 11 capsule after splashdown.) Senokot is still sold in the company's OTC line.

Purdue's entry into the pain space, specifically opioids, came in the early 1970s, after U.K. scientists at Napp Laboratories developed a sustained-release technology, eventually called Contin and initially applied to two successful asthma drugs. Generic competition for Betadine was looming by then, but the next blockbuster franchise was born in MS Contin, an oral, sustained-release form of morphine. Contin-based forms of the other major opioids used in pain, oxycodone and hydrocodone, would follow, and abuse-deterrence became the new imperative in the 2000s.

Now there are four abuse-deterrent products on the market. OxyContin (Oxycodone SR) was reformulated in 2010 to make it more difficult to solubilize or crush. In 2014, three new abuse-deterrent products were introduced: Purdue's Targiniq (oxycodone ER), with a substance to block the drug's effects if the tablet is crushed; Hysingla ER (hydrocodone ER), resistant to chewing, crushing, snorting, or injecting; and Pfizer's Embeda (morphine sulfate and naltrexone hydrochloride) extended-release (ER) capsules with properties designed to reduce oral and intranasal abuse (i.e., snorting) when crushed.

Abuse deterrence may be effective for many patients but the results are not straightforward. Studies show many abusers simply switch their drug of choice, often to the chief illegal alternative, heroin. Sustained release has also had a mixed reception among pain sufferers, some of whom prefer shorter-acting drugs for their flexibility in treating chronic but variable pain. In the pain space, despite a great turnover, a high level of medical need remains.

pain. But so far, nothing has replaced the older drugs except for the extended-release forms pioneered by Purdue and others, such as the former Organon.

Critics say the new forms, which discourage sniffing and injection of crushed pills, do nothing to curb new cases of abuse and addiction, but Purdue has aligned itself with patients in pain who want access, versus advocates who deemphasize the pain-driven need and spotlight the abuse. Some say Purdue helped create a pain market that never before existed. Others, overwhelmingly patients, thank their lucky stars the company and its products exist.

Other difficult decisions have involved painful "restructuring" layoffs in communities such as Stamford, CT, which relied on Purdue for decades. "Our former colleagues made decisions that got us to where we are now," says Timney. "Getting the company to buy into the future vision happened quickly, but the way to getting there is not a smooth road. Part of our strategy was a 'leaning' of the organization, a shrink-to-grow mentality,

which allowed us to reallocate resources to areas where we could build new capabilities, as in business development. We had to adapt to the changing environment, and the organization quickly got that. These were difficult decisions, but they were the right decisions for the longer term."

There is not much debate about the commercial success of Purdue since it embarked on its resource adjustments and enhanced extended-release, abuse-deterrent programs. Timney says without bombast that the company revolutionized the pain-management space and produced one of the industry's greatest success stories — though its privately held status kept it from sharing much of the story with the world.

"Without a doubt, the Purdue business model, focusing on a particular category and a handful of products, has been historically successful," Timney says. "To go forward, we have to evolve, continuing to meet the needs of customers and patients and all of our stakeholders. We state our strategy clearly in three steps: compete, win, and grow. They are actually three overlapping phases."

He explains that the compete step requires assembling and strengthening critical capabilities for doing business in the changing marketplace. Managed care presents an example: "How do we build the right capabilities for the managed care of tomorrow, not the managed care of today?" Or marketing: "How do we build capabilities in the marketing space to befit a 21st century pharmaceutical company, and building upon what we've done in the past, how do we become agile enough to introduce new products into an established system rather than just a pain-focus system?"

Win is a step that demands market leadership, Timney continues, not only in opioids with abuse-deterrent properties, but even broader, such as introducing abuse-deterrence into other therapeutic areas where the need exists. Purdue sells three of only four approved products with abuse-deterrent properties. He cites the CNS area as a logical new target for future company products, emphasizing how it has prepared for such expansion internally and in its stance toward other industry players.

"During the past year or so, we have changed our research model from one which focused heavily on internal discovery; we've virtualized the discovery to be much more externally focused, and we adjusted the size of our internal unit to have a much more flexible R&D structure with a business-development focus. Thus we are much more externally focused, and we're open for partnering. We are able to scan the landscape rather than stay fixated on our internal programs."

The second stage of Purdue's win strategy is attaining a broader leadership position in pain, Timney says. Though successful, the company's focus on chronic pain and opioids has been a very narrow one therapeutically. Purdue is researching new options for pain treatment, including nonopioid medicines and other modes of abuse-deterrence, including those reducing oral abuse. While Purdue already adheres to PhRMA's Principles for Responsible Clinical Trial Data Sharing, the company is exploring new ways to share clinical trial information with key stakeholders.

Partnerships may be the primary vehicles for entering new areas outside pain, says Timney, especially in cases where Purdue can add its franchise-honed skills to the partner's market presence. "We are phenomenally good at complex products, complex marketplaces, and complex customer management. That is usually where Big Pharma really struggles."

Reach Machine

Timney says the company has built its own communications platform to engage with a new crop of stakeholders; namely, investment banks and potential partner companies. "Once we started to open the door for business in new areas, people said they hadn't known Purdue was interested outside of pain. In the past, we have not been an organization that does external deal-making. Now, we are looking at what could be eight to 10 active business development deals."

In the partnering information on Purdue's website, the company lists capabilities that emphasize the breadth and depth of its technology — from discovery tools to formulation, clinical trials, and so forth — making it appear almost CRO-like.

But Timney says the company aims to be much more than a technology supplier to partners.

He observes Purdue has one of the largest specialty/primary care field forces in the industry, with about 550 representatives. "We have the ability to educate multiple stakeholders across many different and difficult areas." For example, many of those reps already call on specialists outside pain, such as oncologists, and could add nonpain products to their kit bag. Similarly, he says the company's R&D organization can apply its extensive knowledge of patients and specialists in those areas to developing nonpain therapeutics.

"We are positioning ourselves for partnering in every possible area, licensing to acquisition, and at any stage of development — partnership in the true sense, whether commercial or development. Nothing is off the table. That is the beauty in the flexibility of being a private company. We really can take this in any way we want."

He says the company's initial aim is to obtain multiple later-stage assets in each targeted area. "This is an important point — if we step outside of pain, we want to build a franchise. Getting just one partnership or one asset in a space is not enough. We need to know where the science is heading and build our innovation upon the unmet need with three or four different types of opportunities in the same space, to spread the risk along our development pipeline."

"During the past year or so, we have changed our research model from one which focused heavily on internal discovery."

MARK TIMNEY
President and CEO, Purdue Pharma

Creating a much broader therapeutic focus for Purdue may help it move beyond the balancing act inherent to its pain franchise — between the traditional pharmaceutical business goal of achieving ever-greater prescription volume, and limiting the misuse that follows as a function of always expanding availability. Beyond abuse-deterrent technology, entering new areas is the only way to grow, the third charge of Purdue's rallying cry.

"We don't want a single prescription other than one written for the right patient, for the right reason, and by the right prescriber. We have developed world-class abuse-deterrent practices in coordination with the FDA, as well as our stakeholders in law enforcement and throughout the healthcare system. But the strategy of focusing more broadly in pain and outside of the opioid space does give us significant opportunities to grow."

At the same time, and despite what Timney argues are systemic barriers to limiting pain-med abuse, he unequivocally confirms the company's commitment to the pain area. "It is important to understand no single policy or product will ever solve a problem as complex as prescription drug abuse. It's multifactorial. But it is also a fast-moving area of technological innovation. The stakeholders, such as the FDA and the DEA, are fully behind it; they want this area of innovation to grow, and our customers realize the value these products can offer in offsetting costs associated with the abuse."

Timney is also clear about Purdue's intended position in the pain market. "Only a few months ago, there was only OxyContin [oxycodone HCI] that had abuse-deterrent properties. But now there are four such products on the market and more than 30 others in development at this point, though not all will make it. The FDA and, I believe, Purdue have set a very high hurdle on what really is abuse-deterrence. We have helped define and shape that. It is greater than one company, but as I keep saying to my organization, that doesn't mean we should ever stop taking a leadership position here."

Window For The World

Is the change at Purdue — restructuring for its march into new territories — merely a clichéd shift in the winds, a meteorological trend fated to skirt along the surface only to vanish in the inevitable counter-wind? Or does its meaning run deeper beneath the company's mantra of compete, win, and grow? Pharma franchises traditionally face less competition than diversified companies. But Purdue has found its narrow space sufficiently competitive to impose evolutionary pressure on the company and motivate its adaptation.

One measure by which the outside world may judge the therapeutic expansion is how much it restores and perhaps increases the scale of operations lost in its restructuring, as well as boosting its revenue and product portfolio size; in a word, grows. Competing and winning should ensure growth — but not always, as they say, in this crazy business.

Another remaining unknown about Purdue: Will constant "transparency" change the private company from a long-term planner to a short-term actor, similar to public companies in the industry? Timney and his team must shuffle the ball carefully if they wish to preserve some of the farsighted strategic benefits of private ownership and silent running. Ironically, some of the largest public pharma companies have been talking about walking behind a corporate screen, essentially becoming faceless mega-holders of incorporeal product brands. The future of either path is even murkier than some corporate minds.

Just as surely as Purdue's present state and recent history, its distant past may have important lessons for today's young life sciences companies. Could a contemporary company, inspired by science, launch itself into business with the same build-a-franchise strategy — maybe buy a small-market commercial company, license in other products in therapeutic clutches, and use the revenues to fund R&D? Actually, the answer is a qualified yes, still playing out in companies such as Sucampo, featured in our March 2015 issue.

Yet, be the answer yay or nay, the question raises important issues, including how far franchise-building may divert a company from its original intent. Still, many start-ups reinvent themselves, and sometimes more than once, heading off in new directions when new science and business paths open up. To such companies, enterprise is as close to the heart of innovation as science. In that sense, Purdue is just beginning. Let us return some day to see its progress a bit further down the path.

Do you have something to say about Purdue, its restructuring, and its therapeutic-area expansion? Please post your comments on-line with this article under Current Issues or Past Issues at lifescienceleader.com.

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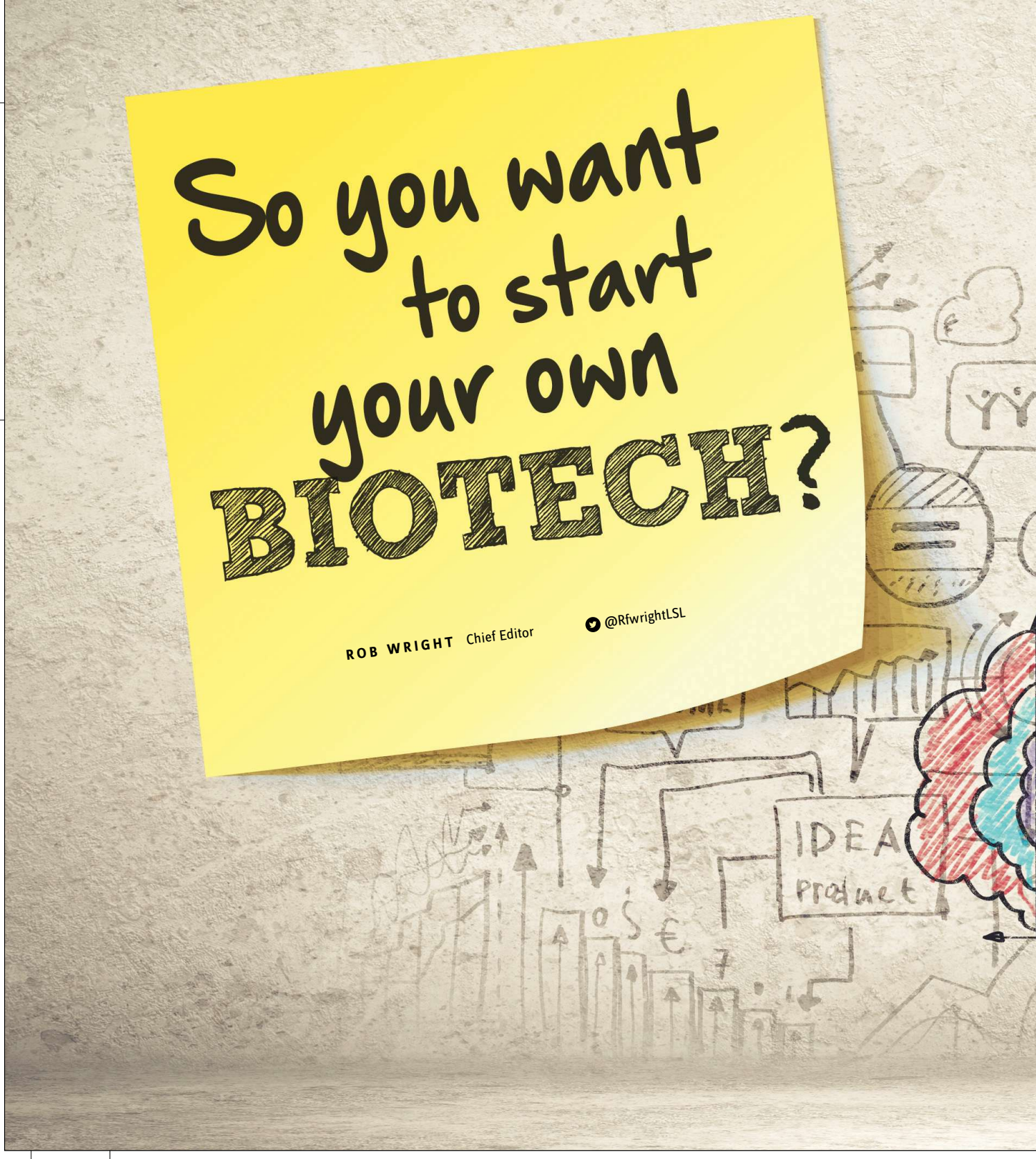


INFORMATION
NEW
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Removing his Stetson, Tony Brazzale steps to the podium. The president and CEO begins his 15-minute PowerPoint pitch for why you should consider investing in Gordian Biotechnologies, his second biotech start-up. It's the kind of presentation that's being given formally *and* informally throughout San Francisco during the week of Jan. 12, 2015, as the city hosts both the 33rd Annual J.P. Morgan (JPM) Healthcare Conference and the 2015 Annual Biotech Showcase.

Brazzale is seeking funding for his company to develop a new generation of beta-lactamase inhibitors to allow existing antibiotics to once again be effective against drug-resistant pathogens. Although his schedule is tight, I convince him to share 15 minutes for an impromptu interview. My goal is to talk with someone who has *been there, done that,* and then share their insights with any of our readers who daydream about starting their very own biotech but have yet to take the plunge.

What's Holding You Back From Taking The First Step?

Many Americans talk about their desire to be self-employed, but only about 6 percent of the population ever act on their longing. What is holding people back? Perhaps it is the often-cited statistic of 80 percent of start-ups failing within the first 18 months. "Don't let this number scare you," says Brazzale. "It [failure] is actually probably closer to 93 percent in biotech."

ARE YOU PREPARED TO SELL THE SIZZLE OF YOUR SCIENCE TO INVESTORS?

JIM HAMBY, PH.D.
Vice President of Business Development for Ash Stevens

Shortly after concluding my discussion with Tony Brazzale, president and CEO of Gordian Biopharmaceuticals, out of the corner of my eye I see Jim Hamby, Ph.D., VP of business development for Ash Stevens, a CMO exhibiting at the 2015 Biotech Showcase. I invited the former Pfizer medicinal chemist with over 25 years of industry experience to share his perspective on what he looks for during investor presentations. "A lot of times it's the technical part that stands out to me," he says. "Do I think it is an important product? Is there a commercial demand for it? Is it something that has solved a big problem? Is there a big unmet medical need? Is it a totally novel idea? Do they have a first-in-class something, with solid-looking science, that's going to beat whatever is out there? Those are the things I look for."

Hamby admits he pays close attention to the science. "Scientists are very detailed and can ask questions that get into the nitty-gritty to understand the technology," he explains. "It's totally different at investor conferences where you usually have a CEO, head of business development, or chief scientific officer often presenting everything in its best possible light." According to Hamby, investors place a great deal of emphasis on the quality of a biotech's leadership team. And while he agrees that demonstrating capable leadership is important, he says not to overlook the significance of being able to credibly present the quality of your company's science. "A few years ago, I was at a meeting where a presenter was saying they had this orally active antisense therapy," he recalls. "No one has ever been able to make these things orally active, and here is this person standing up there saying they had. And yet no one was asking how this was possible. So I raised my hand and said, 'How did you solve this problem, because for years in the industry people have been struggling with this?' And he said, 'Oh, the technical guys did that.'" According to Hamby, someone from a large pharma came up to him after the presentation to thank him for asking such a good question.

Here is an important point for biotech start-ups to understand when giving presentations to investors — the phrase "sell the sizzle, not the steak" was coined by stockbrokers, not advertising or marketing folk. Because this is how investors think, you must be able to sell the sizzle of your science in small digestible pieces so investors can understand and get excited about your company. Compare what you are trying to do to an everyday product or technology the majority of the audience can relate to. Expect the unexpected, such as someone asking a highly technical scientific question. If these kinds of questions are outside your area of expertise, be sure to have someone waiting in the wings who can address them. However, even if it is your area of expertise, you might not have enough time to answer it effectively. In those instances, it never hurts to ask people to meet you after the presentation for additional clarification and questions. By doing so, you'll never have to dismiss questions with an answer like, "Oh, the technical guys took care of it."

Like many entrepreneurs, Brazzale is used to living on the brink of going out of business. So far he's managed to keep Gordian going for a full year on a $50,000 investment. He says if you're going to ask people for money to support your new venture, the most important thing you can do is conduct a comprehensive market analysis. That market analysis should include an industry description and outlook, information about your target market (e.g., distinguishing characteristics of potential customers, size of primary target market, growth forecasts, pricing, gross margins), and a competitive analysis (e.g., strengths, weaknesses, barriers to entry, regulatory restrictions).

"You need to do a market analysis to figure out if your idea is (A) a problem in search of a solution or (B) a solution in search of a problem," he states. "You need to make sure there is a problem. Then, you need to make sure your idea has the potential to solve whatever that problem is." Brazzale uses Gordian Biotechnologies as an example of this process. He explains that he started out as a bench-level chemist in antibiotic drug discovery. "In the 1990s we knew antibiotic resistance was a fast-growing problem that got worse when pharma moved to the blockbuster model and began developing lifestyle drugs and abandoning efforts in antibiotic discovery and development," he says. Though he knew there was a problem and an unmet medical need, it wasn't until he was working with the University of South Florida's Tech Transfer Office (TTO) on a totally different project that he became aware of a possible solution. "They asked for my opinion on an asset within their portfolio described as a nonbeta-lactam containing, noncovalently bound, reversible beta-lactamase inhibitor [BLI] with activity against resistant bacterial strains. Looking at the data, I was fairly confident that this 'had wheels.' Then they asked if I was interested in forming a company around the portfolio and running with it."

That led to the prerequisite negotiations around exclusivity, terms, and licensing, all of which ended up being the easy part of setting up this new company. Brazzale soon discovered that funding would become his biggest challenge. "It's important to recognize that if a TTO is overvaluing an asset, it is often hard to raise money from the bottom of a hole, because the value is created by the company working on the development," he says. "Make sure you are working in partnership with your licensing officer, and maintain a positive relationship with the TTO."

He adds that one of the biggest mistakes biotech start-ups make is confusing the company's value as being the drug. "The clinical value your product brings to patients, and once marketed, returns to investors — *that's* your value," he explains.

Step Two, Build Your Staff

Once you have completed your market analysis, Brazzale says the next step is to surround yourself with people who are smarter than you. "You want people who are experts in the areas where you are weak. You need to understand just enough about what it is they do to be able to translate this information between knowledge silos." Brazzale refers to this as playing to your strengths. One of his strengths is public speaking, a skill that comes in handy when seeking investors. "If you can't present and hold the attention in a room without people falling asleep, then you need to find someone who can, because you will be doing this [i.e., marketing, presenting] — a lot."

How do you find good people? Brazzale says this is where networking comes in. For example, when he needed a CFO, he tapped Peter Gordon, whom he had worked with at his previous company, Melanovus Oncology. He filled other positions with more past colleagues and from recommendations from people he trusts. In 2000, he took a big step in building his professional network when he became a member of the younger chemists committee of the American Chemical Society (ACS). In 2010, he took on the role of public relations chair for an ACS technical division. His advice is to take on similar opportunities to build your network.

HOW TO MAXIMIZE YOUR TIME – AND MONEY – AT TWO KEY BIOTECH SHOWS

Tony Brazzale, president and CEO of Gordian Biotechnologies, believes every biotech start-up CEO needs to attend the JPM Healthcare Conference and the Annual Biotech Showcase in San Francisco. But he says only do so if you have a very strategic plan, and that starts with booking your hotel room early. "You don't need to stay in an expensive hotel," says the budget-conscious CEO. "If you work the show right, you will be in your room only in the middle of the night, anyway." Further, Brazzale says don't be above using public transport or sharing cabs, as either provides the opportunity to practice your pitch while saving you money.

He suggests you start scheduling meetings for JPM right after Thanksgiving. And for the Biotech Showcase, as soon as the partnering system opens up, start doing your research and request meetings. "Often you get the name of the company or person but not enough information to know if you should be bothering them or not. There are some people who will only invest within 10 square miles of a city or a certain disease area," he reminds. Many of the partnering systems are blinded. "Sometimes you're getting emails, sometimes not," says Brazzale. "Try to direct people to contact you outside the system so that if there are no meetings available within it, you can find another good time to meet." You also will find yourself scrambling to try to figure out what receptions are happening and which to attend. You want to make sure you choose the ones that give you the greatest opportunity to network with the people you need as investors or partners. "If you're not conducting six meetings or more a day, you're not having success."

And where do you hold these meetings? Some hotels will rent meeting table space by the hour. However, there are other options, such as Lefty O'Doul's Restaurant & Cocktail Lounge, which is right across the street from JPM. According to Brazzale, you can keep a table at Lefty's as long as you keep buying drinks.

How Are You Going To Finance It?

Of course, there is no single answer to how much money you'll need to start a biotech. The same is true for how to finance your new company (e.g., bootstrapping, friends/family contributions, outside investors, etc.). The more important question, according to Brazzale, is how much money will it take for the risk line to fall below the market line. "That's when you most likely get acquired or licensed," he attests. "But this requires a healthy appetite for risk; it's not for the faint of heart. Investors want you to sweat to see if you're just involved or if you're committed."

For Brazzale, the model is simple: If you're going to fail, fail fast, and fail cheap. Conversely, if you're going to succeed, do so quickly and inexpensively. The way to do either is by reducing risk through good science, conducted by a good team that can generate good data, while wisely using investors' money. For example, when Brazzale was getting started, he used a website called fiverr.com. "Anything for five bucks, though you will have to pay for the premium services," he says. This is where he went to get the company logo designed. For his first trip to a show, he wanted to be sure to have professional-looking business cards with an email address that didn't have the domain name of gmail or aol, but gordianbio.com.

Where To Find The Funds

There are three key conferences Brazzale believes should be on the calendars of every biotech start-up. The first two are the aforementioned JPM Healthcare Conference and the Annual Biotech Showcase. The third is the Redefining Early Stage Investments Conference put on by Life Science Nation in Boston in September. "I found that one to be phenomenally helpful," Brazzale says.

He adds that sometimes you don't even have to pay the often pricey registration fees that accompany industry conferences to still get the value out of them. "Last year when I was forming Gordian, I didn't register to attend any of the conferences, but I went anyway and networked in the lobbies because everybody I knew was going to be there." In fact, being in San Francisco in January 2014 was pivotal to building his board (via in-person meetings) and further strengthening his network.

In addition, he suggests finding a conference that's relevant to your therapeutic area. "Some investors only invest in one therapeutic area." If you have therapeutic expertise, volunteering to moderate a session or serve on a panel can lower your costs. If this is not an option, be sure to register early to get the early-bird rates.

Another tip from Brazzale on finding investors is to read *The Halo Report*, produced by the Angel Resource Institute. "Eighty-five percent of angel investment happens in the angel's backyard, so you need to have some focus on your local angel groups." You can find many of these groups through online searches. But be aware that many angel groups or angel forums are composed of service providers. Brazzale notes service providers as being very important as they are often the trusted advisors to investors. "If you want to get to an investor, it's easier to go through an introduction from somebody they trust as opposed to just cold calling." That being said, Brazzale says you've still got to be willing to do some cold calling.

"The clinical value your product brings to patients, and once marketed, returns to investors — that's your value."

TONY BRAZZALE
President and CEO of
Gordian Biopharmaceuticals

Taking the plunge into starting your own biotech is certainly not easy, nor for everyone. But if you do, Brazzale suggests you consider adopting a mindset similar to that of the Spanish explorer Cortés, who upon reaching the New World is credited with burning his ships as a means of motivating his crew. "Investors are leery of people who are only half in and don't want to work with people who don't have any skin in the game." In other words, if you want to get your "skin in the game," you need to have a no-turning-back mentality when starting your own biotech.

TIPS FOR BUILDING YOUR FIRST BIOTECH BOARD

When building your biotech board, Brazzale has three tips. "Keep the board of directors small," he says. "Because investors are going to come in, and they're going to want a board seat, assuming they bring in enough money." He attests to having gained this wisdom from his experience at Melanovus. His second tip is not to put anybody on your board who's not going to bring value in one way or another. "Some will bring money, others expertise, but all should bring a rolodex of contacts that can choke a horse," he says. Finally, figure out how you are going to incentivize your team, either through equity or payment. "Having a really good incentive program for your board gives people confidence there's going to be a payout at the end of it, especially if they are coming in for equity," Brazzale states. "Then as the CEO, your job is to get out of their way, while making sure they are all working together."

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The Price Wars
FROM ALL SIDES

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

On my first road assignment as an industry journalist in 1987, I visited Burroughs Wellcome in North Carolina's Research Triangle Park (RTP). I had just attended the annual PMA (now PhRMA) Meeting, where many people in the industry crowd urged me to speak with the company about its pricing. BW had announced an estimated $22,000 price per year for the anti-HIV therapy Retrovir (zidovudine), setting off a dramatic reaction by AIDS activists, along with a good section of the public in general, to what was then a record expense for any drug. A short time before I arrived in RTP, the activists showed up at the company's headquarters and chained themselves to a fence outside the front door. Health insurers and managed care groups were also in sticker shock and joined the outcry. So what was my first question to the CEO? "Please tell me, why is the price so high?"

Burroughs Wellcome had obtained acyclovir in a collaboration with the National Cancer Institute (NCI) to screen compounds for activity against retroviruses, setting up the expectation that the company would develop and make the drug affordable and thus thoroughly available to the already large HIV population. BW was owned by the U.K. company Wellcome, a commercial arm of the Wellcome Trust, reinforcing the expectation of a low-cost, public-health-style distribution.

But the CEO, first reluctantly but then forthrightly, answered my question with a compelling account of the extraordinary development, scale-up, and infrastructure the relatively small company had to shoulder for the product — multiplied by the considerable risk factor of introducing a drug with serious side effects into a very sick population. Wellcome was also counting on the drug to help finance its continued research with antivirals. There's a lot more to this story, but I will save it for another day.

The memory of that early experience came back to me recently when the managed care giant United Health acquired Catamaran, a large pharmacy-benefits management company (PBM), and the deal sparked a flash-fire of concern in the biopharma industry. Because PBMs negotiate prices on large drug purchases, the merger signaled a new level of bargaining power by a mega-sized health maintenance organization (HMO), which could mean lower margins for prescription drugs in a patient pool about the size of a small sovereign nation.

United Health already owned the PBM OptumRx, and the addition of Catamaran will reportedly give it pricing leverage over drugs totaling more than $1 billion in prescription sales. More and more, PBMs in the United States seem to be looking like the corporate equivalent of the U.K.'s NICE (National Institute for Health and Care Excellence) and other government-run agencies around the world set up to control drug expenditures. One large U.S. PBM, Express Scripts, previously announced it would not cover Gilead's Sovaldi and Harvoni, two breakthrough Hep C treatments, at the company's price of about $80,000 per course.

Does this trend mean innovative new drugs will now be rejected or reduced to the level of commodities in the United States because payers are gaining socialist-like powers over pricing? Or does it foretell the eventual consolidation of drug pricing authority into a single, government-administered system? In other words, is the long-held nightmare of the biopharma industry — the end of free-market pricing in the USA — coming true? And if so, does it spell the death of innovation in the country that has arguably subsidized new-drug R&D for the rest of the world?

Fair warning: at some points in the following discourse, you may wonder on which side of this debate I personally stand. Be assured that, as always, I am on the industry's side. But there is much more to say, so please read on.

History Answers

Drug pricing is a complex issue, and *Life Science Leader* has readers on all sides of it. Brand-name sellers traditionally resent all forms of managed care; generics companies and their suppliers benefit immensely from managed care's tiered-drug lists, co-pays, deductibles, and of course, generic substitution. More recently, though, the line between brand-name and generics businesses has blurred, and in an interesting twist, suppliers have their own challenges with their clients imposing commodity pricing on outsourced products and services.

Outside of the industry, the big picture is also full of opposing and overlapping views. Patients chafe at the shared costs and tiered lists but also at premium prices

"I confess to feeling some compassion for the payers in confronting the sudden prospect of a huge bill for Solvaldi."

for brand-name drugs, and the argument that a prescription drug is worth more than a pricey consumer item like a big-screen TV has never fazed them. Even for some generics, patients are reporting high price tags and co-pays of late. It is precisely because people need the drug for a condition they don't want to have that they demand to pay as little as possible for it. Payers extoll medical advances in theory — and some have even recently put a bit of cash behind drug development — but they can often be short-sighted in their pinch-penny practices regarding new medicines.

In some ways, none of this ado about pricing is new. There is a long history of managed healthcare and its relationship to the U.S. biopharma industry — a history full of prescribing and pricing restrictions as well as negotiations, discounts and rebates, bundled-product contracts, and corporate consolidation on both sides of the table. Managed care hit the pharma industry in the 1980s, and its power has only grown stronger ever since; almost all U.S. employers with healthcare benefits imposed managed care plans on their employees in the successive decades.

HMO consolidation has always been part of the game, but the big players in managed care are reaching a critical point of power now, not so much because of the current large-scale expansion in health-plan coverage, but because of the increased IT power that allows the HMOs to monitor and control individual physician prescribing behavior. The union of HMOs and PBMs was an early phenomenon, though their origins were separate. At times, PBMs have also allied themselves with pharma companies, encouraging individual physicians to switch products they prescribed. But after decades of growth and consolidation, the HMO/PBM combinations have become that much more powerful, and nothing much stands in the way of their expanding influence.

In most legends, the heroes cannot slay the monsters until they understand them. In business, an equivalent maxim applies: When your customers become more powerful than you, learn everything you can about them and adapt to the pressures they present. Don't try to be the immovable object in the path of an irresistible force.

Driven By Business

Although I've heard managed care described by industry people as "socialized medicine" ever since my first year in this business, it is actually a unique product of the U.S. free enterprise system. It essentially represents the kind of customer consolidation and, yes, blind-eyed bargain-hunting that has affected other industries. I believe the biopharma industry can fight pricing pressure on philosophical grounds, but as long as managed care remains a profitable, growing business, it will continue to exist and biopharma companies will also have to adapt to it.

One of the conundrums the industry will need to address is the acknowledged lack of R&D productivity among Big Pharma companies in general, even during the pre-Recession days of double-digit sales growth and profits in the United States. The industry had never before seen R&D operations at the huge scale created by record spends and mega-mergers beginning in the mid-1980s. Yet the expected boost in new chemical and biological entities from those operations never materialized in proportion to the greater spending. Instead, the bulk of innovation ultimately came from the alliance of academic (NIH-funded) research and private (investor-funded) enterprise.

I first learned of the unique U.S. system of government-industry collaboration in drug research from Dr. George Poste, then the chief scientist and R&D head at SmithKline Beecham, in his keynote address at a PhRMA meeting in the late 1980s. Poste credited the NIH/industry partnership as a driving force in U.S. innovation. As with the polio vaccine and other shining examples of the industry's heroic role in public health, the country had looked beyond politics to forge an effective compromise manifested in an industry-government alliance that turned out to be marvelously synergistic for many years.

Managed healthcare seemed almost sacrilegious when it arrived on the scene, very early introducing P&T (pharmacy & therapeutics) committees, drug formularies and therapeutic substitution, and the other measures already described. When I started writing about managed care about 25 years ago, I got hate mail from industry loyalists who wanted none of it; they just wanted it to go away. The notable exceptions once more proved the rule. But in time, companies began to deal practically with the emergence of something they really had no power to stop, and their managed care marketing departments then grew quickly, typically from small, isolated units of two or three people at headquarters to many more scattered around the country, wherever HMOs and PBMs held sway.

Physician-targeting sales forces, although expanding even faster than R&D in the same period, eventually began to shrink by the hundreds of thousands to what we see today. Meanwhile, direct-to-consumer advertising all but replaced the once-booming medical-journal campaigns, largely in the hope of stimulating enough patient demand to override payers'

prescribing controls. Industry also began to lobby the public heavily, flying the flag of innovation and counting on patients to insist they always get the best possible treatment.

But there was an uncomfortable truth that seriously undercut the industry's position on pricing: For most of the time companies were expanding both sales and R&D, they achieved almost all of their revenue and profit growth through price increases, not by introducing innovative new products. Companies largely blamed the FDA for slowing NCE (new chemical entity)/NBE (new biological entity) approvals, but at the same time, they were acknowledging their own internal problems by cracking down on their R&D people, imposing milestones and metrics in the vain hope of stimulating internal R&D "productivity." Finally, nearly all big companies abandoned the internal "critical-mass" approach and turned to the academic/enterprise alliance (i.e., biotech) for more and more new products.

Battle To Win

Now you may see why I say the pricing issue is complex. At the same time, I believe managed healthcare cannot hold back the real public demand for the kind of therapeutic innovation we have all come to expect, by whatever means the industry manages to accomplish it.

"I would just like to encourage the industry to get over its long-held us-vs.-them, everyone's-against-us mentality."

Already, the principle of premium pricing for products addressing severe unmet medical needs, although currently overused for niche cancer drugs, has been established. Many patients can now challenge their healthcare providers for coverage without fear of losing their jobs, and public pressure on United Health and other healthcare giants will only grow stronger with time.

Yet the ante is also up for the biopharma industry, because routine annual price increases for less-than-innovative products will not fly, at least not without strong payer opposition. And unfettered premium pricing of niche products is probably unsustainable as the dominant biopharma business model.

At some point, I believe this industry will have to focus on broader markets that can produce another classic revenue driver: volume, multiplied by the advantages of an exclusivity period and a relatively profitable price structure. A steady stream of innovative new entities would make all other compensating maneuvers — buying off generics companies, product-driven M&As, etc. — mostly unnecessary.

Cutting costs of care matters to managed care, but it would matter more if HMOs could take out a big low-interest loan on the projected savings. A sudden spike in immediate expense in any business cannot be amortized. (Please, someone tell me if I am wrong about this; perhaps some HMOs do have accounting options for doing just that, though I'm sure they need good evidence to back it up.) I confess to feeling some compassion for the payers in confronting the sudden prospect of a huge bill for Solvaldi. They are accustomed to paying premium prices for niche products but likely not as prepared for products with such a large market as Hep C. As everyone knows who has dealt with the stock market, economics often favor short-term over long-term thinking.

Bottom line: I would just like to encourage the industry to get over its long-held us-vs.-them, everyone's-against-us mentality. I would like to see biopharma companies apply some perspective-taking when negotiating with their business adversaries, even if they hide it behind a poker face. Cognitive scientists say one of the hallmarks of human intelligence is "theory of the mind," or the ability to imagine what's going on in someone else's head. At this year's DCAT Week, one speaker said "knowing what the other person wants" is the first essential step in any negotiation.

Still, I'm not advocating perspective-taking merely as a negotiating tactic. I just ask the question: How will the industry ever get the love it wants and deserves from the public if it continues to isolate itself from the rest of society behind an air of resentment? It might be very effective to take the opposite approach — come to the bargaining table recognizing the effect your position might have on the other's business. Come to patients acknowledging cost as a potential barrier to access. Try to avoid a situation where your price could look like a ransom — or at least be prepared to explain and justify it with equanimity.

Meanwhile, the industry as a whole should focus on the battle it could win — against the commoditization of pricing for innovative medicines, including specialty drugs that boost safety, efficacy, and compliance. Keep the focus on real, tangible innovation and be ready to bargain — even if (deep breath) the big bad specter of the single, central payer somehow replaces the present U.S. system. The industry and its supporters can make a strong case for protecting innovative biopharma as a public-health treasure worthy of generous rewards that also help ensure integrity, reliability, and trustworthiness of companies in the sector. The rest is negotiation.

So, you might ask, which side of the Price Wars am I on?

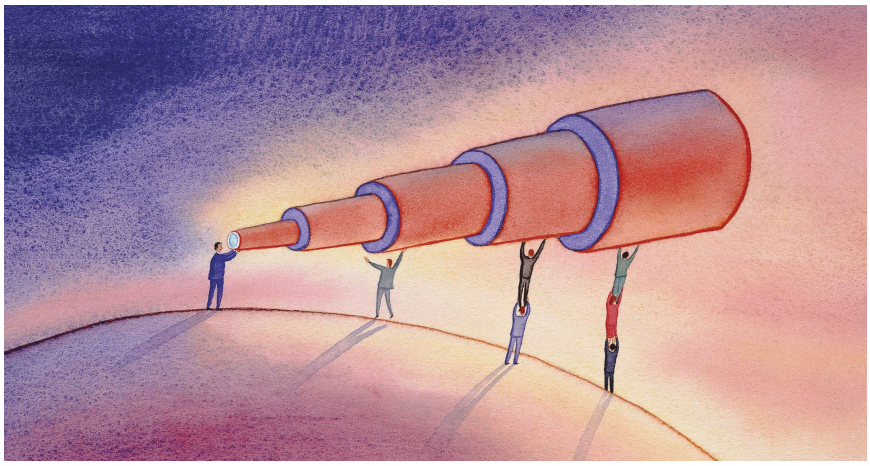
I am on all sides.

P.S. Whether you agree or disagree with the points I've made in this article, you may have your own say in the matter by emailing me or by posting a comment on the page for this article on our website.

Remote Clinical Trials: A Goal Just Over The Horizon

BY NEAL LEARNER Contributing Writer

People don't think twice to pay bills on a smartphone, share experiences on social media, and even monitor sleep habits on wearable activity trackers. But when it comes to participating in a study to test a new therapy or medical device, we might as well be standing in line at the bank to deposit a paper check.



Clinical trials today look pretty much the way they did 25 years ago, with patients required to make regular trips to clinical research sites for in-person testing and hand-entered data collection.

Conducting remote clinical trials, by contrast, would bring the antiquated process into the twenty-first century, providing the kind of convenience and cost-saving efficiencies that other industries now take for granted. Study volunteers could report their data from home via mobile technologies directly to systems that would gather and analyze the figures in real time, while researchers could interact with patients via online portals to ensure they stay engaged and active.

Such an approach, while feasible, is still years off, most experts say. "The remote clinical trial seems a little bit like the horizon, an imaginary line that moves farther away the closer you get," says Andreas Koester, VP of clinical trial innovation at Janssen Pharmaceutical Companies, a part of Johnson and Johnson.

That's not to say we'll never get there. Koester expects to see a much broader adoption of mobility technology in the trials process over the next three years. "The tipping point is almost here," says Koester, an R&D veteran who also serves on the operations committee at TransCelerate BioPharma, a nonprofit organization working to find solutions to industrywide R&D challenges. "Every day you see some company piloting individual aspects [of remote technology/components] into trials. That's the way innovation works. You start by utilizing remote technology for individual aspects, and in doing so, you learn what process changes are required."

EUROPE'S FIRST FULLY REMOTE TRIAL

One company pushing the remote trial space is U.K.-based technology and consulting firm eClinicalHealth Limited, which in February announced that the European Medicines Association's ethics committee had approved the first fully remote diabetes trial in Europe. The Finnish-based VERKKO trial, conducted in collaboration with communications firm Langland, device manufacturer Mendor, and drugmaker Sanofi, is studying Mendor's 3G wireless blood glucose meter with a glucose-profiling technology.

"So far all of our expectations have been exceeded," says Kai Langel, cofounder of eClinicalHealth. "The patients appear to be more compliant than those in a sister trial that was done on paper. That's really impressive because these patients used to get one-on-one instruction from the patient site. Now they do all of that online, and they're doing better than they did in the previous study."

But that's not to say everything went perfectly. One of the biggest challenges the trial faced initially was educating some less-than-computer-savvy volunteers. Simple things, such as finding an email with the account activation link, required additional support. "If you have a big study and you put all of this burden

on the trial site, then it's a lot of work," Langel acknowledges. "It's important that sites have the right kinds of partners that can take over some of this routine management."

But once these details are covered, the advantages of remote trials are obvious. First, there is the convenience this model provides by removing the burden of taking time away from work, school, or family life to visit a research site. And second, counterintuitively, is the ability of the technology to make volunteers feel more connected.

With traditional clinical trials, "Either there are too many visits, and it's a big burden, or there are too few visits, which makes the volunteer feel completely disengaged, and they don't see why they should continue with the trial," Langel says.

Another key advantage is the ability to monitor data in real time and make corrections where necessary. For instance, a patient may have to take measurements at very specific times during the day. With the remote technology, Langel explains, sites can see when someone is doing something wrong with the glucose monitor, such as taking the measurement too late after lunch. "Now we can actively reach out and manage them in real time. We can contact them and say, 'Hey, Mr. Patient, we're seeing you're doing your measurements 15 minutes too late. So will you please change your schedule or measurement time a little bit, and then you'll be fine,'" Langel says. "In a traditional trial, that kind of problem would be detected in the next visit, and then it would already be too late because all of that data would have been taken at the wrong time, and you couldn't use it."

FILLING IN THE "WHITE SPACES"

That point is echoed by Janssen's Koester. Clinical trials today only capture a snapshot of the patient's health during the office visit — a snapshot that researchers hope will give them an idea about the patient's condition over time. "It's quite a crude measure, and it's something that exists because we didn't have anything better," Koester says. "With the advent of devices [e.g., smartphones], we have the ability to fill the 'white space' between the snapshots and really measure the continuum of the patient's condition and the influence of diet, lifestyle, and other parameters, which are right now considered to be imponderables on the evolution of the patient's condition."

Take rheumatoid arthritis, for example. In an office visit, a doctor can measure swelling, physical function, and inflammation

parameters. With remote technology, a researcher could measure improvements in pain and inflammation, as well as improvements in physical activity and the ability to do certain things at home. "Right now we have to rely on patient-reported outcomes, which are a good, but still subjective, parameter," Koester says. "Now we have the opportunity to measure the impact [of the treatment, drug, etc.] on the patient's life."

And highly sophisticated technology exists to do this. Variable sensors and devices exist that can measure everything remotely from blood pressure to blood glucose levels. One in 10 adults in the U.S. already carry a Fitbit or similar device. And there are plenty of technology companies today aimed at providing these services. For example, simple devices are available that don't require the use of a blood pressure cuff, which can be error prone, Koester says. You simply press two fingers on a little device that takes your measurement. And because it happens in a relaxed home environment, the reading is much more accurate than a measurement taken in a doctor's office, where patients often have elevated blood pressure due to anxiety and other factors. "If we had validated all of the systems, a blood pressure trial could be one of the first to be run completely remotely," he says.

MAINTAINING PATIENT-RESEARCHER RAPPORT

Ken Getz, associate professor and director of sponsored research at the Tufts Center for the Study of Drug Development, says interest in remote trials is part of a broader patient-centricity movement to support patient engagement, improve convenience, and increase a patient's feeling of being a partner and active participant in the study. "Companies are really testing and considering a whole host of approaches to try and see if they improve completion and retention rates," he says.

But Getz cautions that designing trials in a way that eliminates face-to-face interactions could damage the patient-investigator rapport that is critical to clinical research. Volunteers could lose interest and drop out. "Interfering with that relationship between the study staff and study volunteer is something we have to treat very, very carefully," he says.

> *"Right now we have to rely on patient-reported outcomes, which are a good, but still subjective, parameter."*
>
> **ANDREAS KOESTER**
> Janssen Pharmaceutical Companies, a part of J&J

The goal, Getz adds, is to design a study in such a way that you can get the face-to-face meetings at critical junctures, and where you can also collect data on an ongoing basis using remote technology.

BENDING THE $2.6 BILLION R&D COST

As in other industries, cost factors may ultimately drive change in the clinical trials arena. Bringing a drug to market now costs roughly $2.6 billion and requires a 10-year R&D commitment, according to the Tufts Center. The biggest cost drivers in a clinical trial are the office visits. "If we can do that not just remotely, but in an automated way, you save on checking and double checking for manual entry errors," Koester says. "I think it is easy to see that there is a huge potential for cost savings."

But those savings are actually just a nice side effect for Koester. The real driver behind remote trials is making the experience easier and less burdensome for patients, and in doing so, increasing access for the general population to clinical trials.

Langel agrees that cost savings alone is not the key selling point to the approach. Nevertheless, potential savings are closely linked to the convenience the trials provide. "Because the study is more attractive to patients, and they're less likely to drop out, you can start your study faster, you can get patients through the study faster, and you can wrap things up faster, so that will save you operational costs," he explains. "The average operational cost is about $1 million per month, so if you can wrap things up one month earlier, that's $1 million in the bank."

Conversely, you can tell quickly if the trial is not working. "So instead of running through the whole thing and saying, 'Whoops, we've just spent $500 million, and this is not working,' you can do that after the first month and see which direction things are going."

ONUS IS ON PHARMA COMPANIES

While the advantages of remote trials seem obvious, change comes slowly in the ever-cautious pharmaceutical industry. A widely watched remote clinical trial started by Pfizer in 2011 folded a year later due to a lack of volunteers. Langel asserts that Pfizer's use of multiple mobile and Web-based platforms made it difficult to identify and recruit patients. This problem can be addressed, he added, by using one integrated site for various tasks, including patient recruitment, electronic informed consent, patient communications, and patient-reported outcomes and measurements.

Getz says there was initial excitement around the Pfizer study, and that its failure to enroll study volunteers has caused people to rethink their initial exuberance. "There is much more caution now than we saw 18 months ago as the realities and challenges of implementation really begin to present themselves," he adds.

What is needed to accomplish remote clinical trials is a complete overhaul or reengineering of the clinical trials processes. "The onus is on us — the pharma companies — to integrate these kinds of solutions into our clinical trials," Koester says.

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Search For New Therapeutic Targets Turns To "Loss-Of-Function" DNA Variants

CATHY YARBROUGH Contributing Writer @sciencematter

Fifteen years ago at a White House ceremony announcing the completion of the Human Genome Project's draft of the human DNA sequence, President Bill Clinton told the audience of industry and academic leaders, government officials, and journalists that "today's historic achievement is only a starting point. There is much hard work yet to be done."

Some of that hard work was presented at the Future of Genomic Medicine (FoGM) VIII conference, March 5 and 6, in La Jolla, CA. More than 550 researchers and clinicians from 10 countries, including the U.S., attended the meeting, organized by the Scripps Translational Science Institute in La Jolla. The topics of the 25 conference presentations ranged from prenatal testing to President Barack Obama's Precision Medicine Initiative.

Like other scientific meetings on genomics during the past decade, the FoGM conference demonstrated that, in retrospect, President Clinton's comments were incredibly accurate. The so-called "promise" of the Human Genome Project — a bonanza of new and improved drugs for virtually every serious disease — has not yet been achieved because the human DNA sequence has proven to be stubbornly complex, much more indecipherable than researchers could have realized in 2000. There are obvious exceptions, of course, such as the FDA-approved drugs gefitinib and erlotinib that target genetic mutations common to many lung cancers. And, in diagnosis, "we are in the middle of a revolution in prenatal care," said FoGM speaker Diana Bianchi, M.D., geneticist and neonatologist at Tufts University School of Medicine in Boston. Because of advances in genomics, prenatal genetic testing can now use blood samples obtained from pregnant patients rather than amniotic fluid, which is obtained by amniocentesis, a much more invasive procedure.

Since the launch of the Human Genome Project, scientists in both industry and academia have been searching for deleterious mutations, the DNA variants that significantly increase an individual's risk for developing a chronic disease such as type 2 diabetes (T2D). A second category of human genetic mutations also provides potential targets for drug development. These are the naturally occurring loss-of-function (LOF) DNA variants that are protective against specific diseases without causing ill effects. "There is a lot we can learn from nature about disease prevention," said Eric Topol, M.D., FoGM conference chairman and STSI director.

Although LOF gene variants were not a dominant theme of the FoGM meeting, their value as potential therapeutic targets stood out. Mark McCarthy, M.D., professor of diabetes at the University of Oxford, U.K., briefly spoke about the recent discovery of the LOF mutation in the gene *SLC30A8* that protects individuals from T2D. Pfizer is investigating the LOF gene variant in T2D drug development. Scientists from Sangamo Biosciences and Regeneron Pharmaceuticals told how LOF gene variants have led to the design of two innovative therapeutics, one of which may be approved this summer by the FDA.

"You start with a naturally occurring variation, and then you aim to recapitulate it to create a disease-protective genotype and then a phenotype in a clinical setting," said conference speaker and Sangamo team leader Fyodor Urnov, Ph.D. He and his team at Sangamo used a naturally occurring LOF variant in the *CCR5* gene to design a very different therapeutic against the human immunodeficiency virus (HIV). Sangamo's experimental therapeutic, SB-728-T, now in Phase 2 clinical trials, recapitulates the LOF protective genetic mutation that is estimated to occur in about 1 percent of the Caucasian population.

GENOME EDITING APPLIED TO HIV

The *CCR5* LOF mutation was detected several years ago when an HIV patient's cancer was treated with a bone marrow transplant using donor cells. After the transplant, the patient's viral load quickly dropped, and his T-cell count soared. The patient's dramatic improvement was subsequently attributed to the LOF mutations in the *CCR5* genes of the donor's cells. The cells had two copies of the LOF mutation, one from each of the donor's parents.

CCR5 genes code for the *CCR5* protein receptors on the surface of T-cells. To invade T-cells, HIV first must lock onto these receptors. However, in individuals whose *CCR5* genes have natural LOF mutations, the cell receptors are disabled. As a result, HIV cannot infect their T-cells, and they are naturally resistant to HIV infection. By using cutting-edge genome-editing laboratory technology, Sangamo scientists succeeded in inducing LOF mutations in the genomes of T-cells from HIV patients. Urnov explained that as a

result of the editing, the *CCR5* receptors on the T-cells were disabled, and the genome-edited T-cells did not become infected with HIV when experimentally exposed to the virus in laboratory cultures.

Thus far, more than 70 HIV patients have been experimentally treated with their own genome-edited T-cells. The edited cells are administered by infusion. "The treatment has been well tolerated," Urnov said. Clinical trial results indicate that genome-edited T-cells can persist for as long as 250 days post-infusion. The T-cell counts remained high even in the subset of patients whose prescribed antiretroviral therapies were briefly discontinued for 12 weeks on the 28th day after infusion. Long-term viral control occurred in 24 patients, he added.

Sangamo's HIV therapeutic is a proprietary technology that uses zinc finger nucleases (ZFNs) customized by the company's researchers. In the clinical trials, thus far, ZFNs were used to edit the *CCR5* genes of T-cells removed from the patients' blood circulation. In an upcoming Phase 1 trial, Sangamo's ZFNs will be employed to edit the genomes of stem cells harvested from HIV patients' bone marrow. These stem cells are precursors of blood cells, T-cells, and other immune system cells. In addition to HIV, Sangamo has targeted sickle cell anemia, transfusion-dependent beta-thalassemia, and other hemoglobinopathies. The company's scientists have tailored proprietary ZFNs for each of these diseases.

The clinical studies of Sangamo's ZFNs for HIV are the first patient studies of a genome-editing therapeutic for any condition. Genome editing, which enables researchers to disable a targeted gene as well as precisely insert a DNA sequence into the genomes of human cells in laboratory cultures, is a "transformative, disrupting technology," said conference speaker Keith Joung, M.D., Ph.D. With the technology, researchers also can create laboratory cell lines with the same characteristics of diseased patients' cells. These cell lines are ideal for disease modeling and screening of experimental compounds, added Joung, associate professor of pathology, Harvard Medical School and cofounder of the new genome editing biotech company Editas Medicine. Joung also spoke about the epigenome-editing technologies that he and other researchers are employing to investigate the genomic factors that regulate human gene expression.

"LOSS-OF-FUNCTION" GENE IN HEART DISEASE

Another LOF genetic mutation that has led to a novel therapeutic is the variant of the

PCSK9 gene, which normally encodes a protein whose actions help raise blood levels of low-density lipoprotein (LDL), the so-called "bad" cholesterol. Pfizer, Lilly, Amgen, Regeneron, and Sanofi are among the biopharmaceutical companies that have targeted the *PCSK9* LDL as a therapeutic target. The closest to the finish line of achieving an FDA approval are Regeneron and Sanofi, which have been working together. Their *PCSK9* inhibitor is a fully humanized mouse monoclonal antibody.

In January 2015, the two companies' BLA (biologics license application) for their inhibitor, alirocumab, was designated for priority review by the FDA. The agency is expected to formally respond to the application in July 2015, said FoGM speaker George D. Yancopoulos, M.D., Ph.D., founding scientist and chief scientific officer of Regeneron. If approved by the FDA in July, alirocumab will be the first in the new class of *PCSK9* inhibitors. The second-in-class may be Amgen's *PCSK9* inhibitor, evolocumab. The FDA is scheduled to respond to Amgen's BLA in August 2015, said Yancopoulos. "Amgen has been on our heels the whole time," he jokingly told the FoGM audience.

Several weeks after the FoGM meeting, researchers reported in the *New England Journal of Medicine* that alirocumab and evolocumab reduced by over 60 percent the LDL levels of heart disease patients in clinical trials. The results concurrently were presented at the American College of Cardiology's annual meeting. *PCSK9* inhibitors, administered by injection, are designed for patients with high blood levels of LDL cholesterol who cannot tolerate the cholesterol-lowering statin drugs or for whom the statins have been ineffective.

PCSK9 inhibitors originated with the 2003 discovery of a French geneticist who was studying the genetics of a family, many of whose members died from cardiovascular disease at an early age. The scientist linked the family's high blood cholesterol levels to a gain-of-function variant of the *PCSK9* gene. Subsequently, U.S. researchers identified the LOF variant of the same gene in a subset of 300 African-Americans with very low levels of blood cholesterol, explained Yancopoulos.

"We think we're getting pretty smart about understanding genomics and functional aspects of how the genome works, but we're just scratching the surface."

FRANCIS COLLINS, M.D., PH.D.
NIH director

"Alirocumab is the first Regeneron drug that recapitulates an LOF genetic mutation, but hopefully not the last," commented Yancopoulos. To identify other LOF drug targets, Regeneron in 2014 launched a first-of-its-kind collaboration with the Pennsylvania-based Geisinger Health System that eventually will include 100,000 patient volunteers. In addition to new LOF variants, the five-year program will search for the gain-of-function mutations that magnify an individual's risk for developing disease.

PRESIDENT OBAMA'S 1 MILLION PATIENTS

The patient volunteers, whose identities are concealed from the company's researchers, agree to allow their DNA to be sequenced and genotyped. Because Regeneron researchers have access to the volunteers' electronic health records, they are able to search for patterns suggesting possible links between genetic factors, disease occurrence, and health outcomes. During the first year of the collaboration, almost 250 LOF genetic variants have been identified and are under study in Regeneron's labs.

"The identification of new LOF genetic variants is one of many objectives of President Barack Obama's $215 million Precision Medicine Initiative (PMI)," said NIH Director Francis Collins, M.D., Ph.D., who spoke at the FoGM conference. Government funding for the PMI, which was announced by President Obama in his State of the Union address in January 2015, will be included in the White House 2016 budget proposal to the U.S. Congress, said Collins, who added that the details of the initiative are "in the process of being defined."

PMI's centerpiece will be a study of 1 million Americans who will be asked to voluntarily provide blood samples for extensive genomic, metabolic, proteomic, and microbiomic testing. The test results, along with behavioral data gathered from smartphones, Fitbits, and other digital devices, will be linked to the patients' electronic medical records. "This large-scale cohort will give us access to the deep information and power that we've not had before," said Collins, who described the cohort as the "quantified self, multiplied by a million." The "quantified self" refers to comprehensive self-monitoring with digital devices and other technologies.

Collins added that the longitudinal study will be a "phenomenal foundation platform for testing all manner of interventions," including new drugs. Many of the volunteers will come from existing study cohorts such as the patient population of the Geisinger Health System.

President Obama's new initiative could help unravel the complexities of the human genome. "Where we are right now, we think we're getting pretty smart about understanding genomics and functional aspects of how the genome works," said Collins. "But we're just scratching the surface." Referring to a future FoGM conference, Collins may have provided a clue about the many years of research that will be required to make genomic medicine a day-to-day reality. He said that if the speakers at the FoGM conference in 2027 review the presentations of the 2015 meeting, they would say, "We were really ignorant about so many things."

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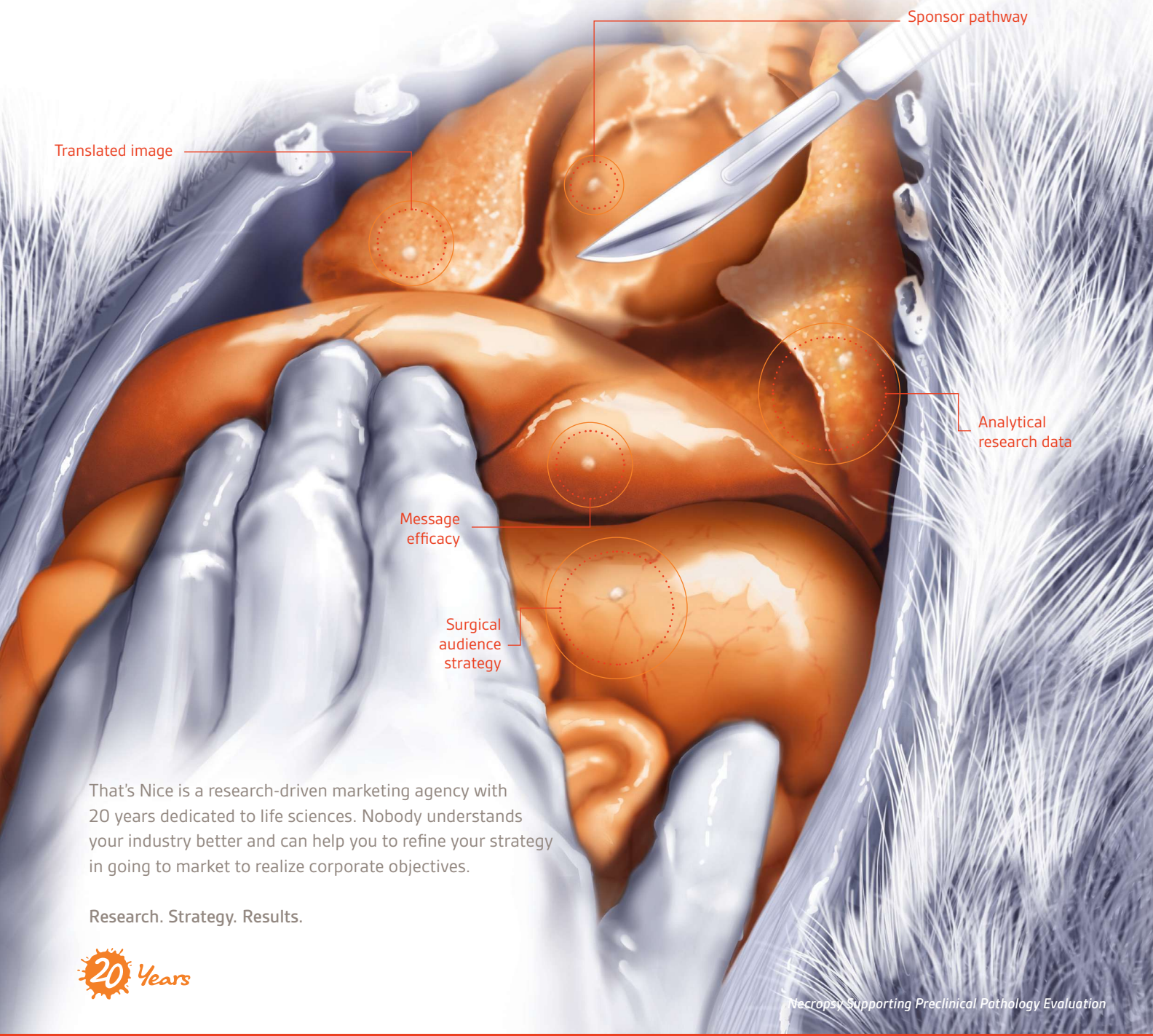

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Drug Development In The Age Of Social Media

K. JOHN MORROW JR., PH.D Contributing Writer

A young, energetic biotech; a promising drug with encouraging Phase 2 data; a young patient population; a disease target for which there is no successful treatment.

What could possibly go wrong?

A lot, it turns out.

That's what Kenneth Moch, former CEO of Chimerix, found out early in 2014 when his company became entangled in a controversy over access to its experimental drug, brincidofovir. A year later, Moch is gone from the company, but he remains eager to share his views on the so-called "compassionate use" of drugs that are still in the midst of their approval process.

In March 2014, Chimerix was carrying out a Phase 3 trial of brincidofovir for the prevention of cytomegalovirus in immunocompromised adults, based on positive Phase 2 results. Early encouraging reports on a trial with another virus, adenovirus, had trickled out in the literature, and doctors at St. Jude Hospital in Memphis, TN, requested the drug for Josh Hardy, a pediatric stem cell transplant recipient with a life-threatening adenovirus infection. After initial refusals for compassionate use by the company, Hardy's parents took to social media, unleashing a deluge of tweets, phone calls, and acerbic emails to the company. The continuing storm of negative publicity quieted only after Chimerix set up a new Phase 3 trial for the treatment of adenovirus, with Hardy as the first enrollee.

ASSESSING THE FALLOUT

Interviewing Moch now, my first question concerned the child's current condition. According to Moch, Hardy's recovery has been spectacular. "His mother blogged about his status, and he had responded incredibly well to brincidofovir," Moch stated. He is now approaching his ninth birthday, and while he still has medical issues, these do not seem related to adenovirus. He has faced multiple bouts with cancer, and his immune system is still recovering from his stem cell transplant, but his family states that he is progressing well.

Moch explained to me that he dislikes the term compassionate use because it implies that if you don't allow the use of an experimental medicine, then your company isn't considered compassionate. "I prefer 'early access to an experimental medicine,'" he said. "The FDA calls it 'expanded access.'" How this process works depends on many different parameters. Each disease, each drug, each clinical trial development plan is different.

Moch feels that there are a number of important lessons for CEOs and corporate leadership. Management teams must prepare for these various issues, especially in the era of social media and patient advocacy. Based on the events that played out over this past year, Moch focuses on what has been learned about the ethical issues, since this is at the very heart of the matter.

SETTING THE GUIDELINES FOR ACCESS

Moch queried, "What do you do when someone calls and says, 'We have a dying child, and it's your responsibility to make treatment available'? The question I ask people to think about is how to balance concern for a single patient, such as Josh, against the needs of many future Joshes? If something happens which slows down the clinical development timeline of a drug, then a large future group may not get access to the therapy. That is the essence of the moral dilemma."

Moch recognizes that there is no formulaic model for expanded access. This means that every company has to think through its own specific strategy, based on multiple parameters. Is the drug a small molecule or a complex macromolecule in limited supply? What are risks to the mission-critical aspects of the clinical development program? Does the drug sponsor have the skills and resources to manage an expanded access program? What is the company's relationship with

the regulatory division of FDA, as each division is different? "There are so many factors, and in my opinion, there is not a single answer," he stated.

I asked Moch whether setting a high bar for access to a drug, excluding all but the most serious cases, would work.

"Well, no," he responded. "The problem is that most criteria have an element of arbitrariness that is going to be challenged. For instance, you say it's only for 18-year-olds and over, but then a 17-year-old shows up, and you bend the rules. What then for a 16-year-old? I don't think there are any bright lines in the decision-making process."

Throughout our conversation, he emphasized that each company needs to think through every parameter of its expanded access strategy. This includes the option to simply not make a drug available. A company may have to consider expanded access. There may be concerns such as the potential for unanticipated side effects, but there are issues of equality of access as well.

REGULATORY AUTHORITY AND THE RESPONSE TO SOCIAL MEDIA

In the coming years, drug developers will grapple with a wave of new regulations. Eight states have now passed "right to try" laws. Their premise is that access to experimental medicines is a "fundamental right." It clearly is a desire, but is it a right? One assumption of "right to try" supporters is that an experimental medicine's safety profile is fully known after Phase 1. Moch asserts that this is simply not the case. Moreover, the request for a drug may be for an indication other than the primary clinical testing focus. Very little may be known about how the drug will work in these terminally ill patients, increasing the risks to the survival of the clinical development program. Management teams will have to balance the immediate need of a patient versus the needs of many future patients.

According to Moch, none of the laws being considered can force companies to give out the drugs in question; rather they are essentially "right to beg" laws, in the words of bioethicist Arthur Caplan. The "right to try" simply says the patient has a right to ask. Doctors are indemnified, so they are not liable for any untoward results.

In the Hardy case, Chimerix had been in conversations with the FDA about adenovirus when it started the new Phase 3 adenovirus trial. This is an important distinction. Chimerix's outcome is not representative, and Moch does not think it should be used as an example of what can happen in the future. Nonetheless he cites some fascinating learning experiences. He feels that he built a positive relationship with the person who led the social media campaign, who had stated that it was his intent to destroy the company and Moch along with it if Hardy had not gotten the drug. After the Hardy campaign, Moch's adversary was asked to be an arbiter of several similar cases. As other families came to him, he realized that he was now making life and death decisions. So he came away with a completely different attitude.

"The problem is that under the glare of social media, you can state a thoughtful, ethical position, but few people care. People just want the drug right now," Moch concluded.

HOW TO TALK TO THE PUBLIC

We then discussed the level of sophistication of the patient advocacy groups. Do they understand the complexities of these issues?

Moch observed that patient advocates and advocacy groups run the gamut in their understanding of the drug development process. Some are well-versed, driven by science and logic, while others feel the only way they can make their point is to take extreme positions. This variability may be seen even in different groups that focus on the same disease.

He mentioned the example of the history of HIV therapy. Some of the AIDS advocacy groups realized that if everyone got experimental drugs, it would have made clinical trials and the ultimate approval of drugs impossible.

But will social media, because of its emotional power, always win out? Doesn't this mean there's a whole new set of problems?

Moch does not believe so. He feels that every company must prepare, and every situation is likely to be different. In the Hardy case, which was the most aggressive use of social media to date, Moch learned in hindsight that several of the advocates were trial lawyers, and their absolute intent was to demonize and vilify in order to get the drug.

"Under the glare of social media, you can state a thoughtful, ethical position, but few people care. People just want the drug right now."

KEN MOCH
Former CEO of Chimerix

"They did not give any credence to the concerns about risks to the drug development process. Look at it this way — what if a patient in an expanded access program suffers a very bad outcome?"

Moch believes that Hardy's case was special in that he had a rapid and positive response, but what would have happened if he had had a rapid and negative response? How would that have affected the public perception of the drug? If clinical development were slowed because other patients declined to enroll in a trial, then the company has made a life-and-death decision affecting future patients. If he had succumbed, would that have negatively affected the view of the drug?

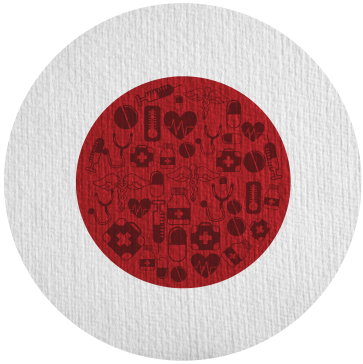
These questions will be confronted in the years to come, but we concluded the conversation by discussing Moch's plans for the future.

"I have been fortunate that five of the six companies that I have been with were successful. I am continuing to look for an opportunity, not a job. There are lots of jobs, but few opportunities."

Japan's Take On Regenerative Medicine: Early Commercialization, Early Reimbursement

GAIL DUTTON Contributing Writer @GailLdutton

New regulations accelerating the approval of regenerative therapeutics in Japan took effect Nov. 25, 2014, propelling that nation onto the radar screens of life sciences companies around the world. The chief benefit of these new rules is that they enable companies to receive conditional marketing approval and generate revenue from regenerative products while trials are being conducted.



"A lot of people here (in the U.S.) don't know about it," says Gil Van Bokkelen, Ph.D., CEO and chairman of Athersys and ex officio chair of the Alliance for Regenerative Medicine. "As more visibility and tangible progress is generated, I think it will create a lot of additional interest and excitement."

The acceleration of regenerative medicine development and commercialization is part of the economic revitalization plan – "Abenomics" – launched by Prime Minister Shinzō Abe in 2012. That plan also includes ¥110 ($1 billion) in funding for stem cell research.

"Regenerative medicine is a huge issue for Japan. Half the population is over age 50, but regenerative medicines have been limited because of the difficulty getting through Japan's Pharmaceuticals and Medical Devices Agency (PMDA)," notes David Hall, CEO, RepliCel.

For example, Karine Kleinhaus, M.D., MPH, divisional VP for North America at Pluristem Therapeutics, explains, as of May 2014, there were only two approved allogenic cell therapy products and fewer than 15 clinical trials. "Japan's goal is to increase the number of approved cell therapy products, expand targeted indications, and extend its capabilities from manufacturing to bedside. Partnering interest from Japanese pharmaceutical companies is strong."

TWO NEW REGENERATIVE MEDICINE LAWS

Japan's new regenerative medicine legislation is actually two separate laws. Law No. 84/2013 amends the Pharmaceutical Affairs Act, renamed the Pharmaceutical and Medical Device (PMD) Act, and pertains to the commercial development of regenerative therapeutics. Law 85/2013, the Safety of Regenerative Medicine Act, deals with clinical and physician-led research.

The PMD Act defines regenerative medicine as cultured or processed human or animal cells, or transgenic cells, used to reconstruct, repair, or form structures or functions in the human body, or to treat or prevent human diseases.

Gene therapies also are covered by that act, providing they are at least equivalent to cellular and tissue-based products and meet either the FDA definition of gene therapy or the EU definition of advanced-therapy medicinal products.

This law speeds therapeutics to market by allowing conditional marketing authorization. For example, Hall says, "A 20-person trial that shows safety and is predictive of efficacy is sufficient to get conditional approval for seven years, without needing placebo trials. Efficacy will be determined by the market. The new regulations dramatically change the pathway toward revenue."

During the seven-year conditional approval period, companies are expected to continue filing data. By the end of that period, they must either apply for final marketing approval (the equivalent of a BLA [Biologic License Application]) or withdraw the product.

The companion law, the Safety of Regenerative Medicine Act, governs clinical and physician-sponsored research. It allows cells to be processed outside hospitals for safer and faster manufacturing. Oversight is provided through tier-based, risk-dependent analysis, and through accreditation of cell-processing centers.

JAPANESE TRIALS NICE BUT NOT NECESSARY

"Our understanding of the PMD Act is that the PMDA is looking for more than just a Phase 1-type analysis. It would like to see a record of safety and some meaningful evidence of therapeutic benefit,"

Van Bokkelen says.

In effect, that means "The option of going to market is after a solid Phase 2 trial," Kleinhaus concludes. "Meanwhile, postcommercialization and observational studies must be conducted."

"We are likely to see a meaningful increase in clinical trial activity in Japan as a result of this new framework," Van Bokkelen says. Although the regulations don't specify that trials must be conducted in Japan, the PMDA is clearly guiding sponsors toward running a clinical trial in Japan.

"Policymakers in Japan realized regenerative medicine has tremendous potential to address serious areas of unmet medical need that impact their national healthcare system," Van Bokkelen says. "By encouraging clinical development, they simultaneously are promoting innovation, the creation of more effective healthcare solutions, and economic development."

WESTERN COMPANIES IN JAPAN

A handful of companies have ventures underway in Japan, including Athersys, RepliCel, Pluristem, and Mesoblast.

The new regulations already have affected Athersys in a major way. In March, the company announced a partnership with Japan's Chugai Pharmaceuticals to develop MultiStem to treat ischemic stroke patients in Japan. That deal's potential value exceeds $200 million even before double-digit royalties and payments for manufactured products are added. "That deal might not have happened without Japan's greater emphasis on regenerative medicine," Van Bokkelen says.

Athersys began laying the groundwork for this deal soon after the bills passed the Diet (Japan's bicameral legislature), working with Japan's PMDA to prepare to initiate clinical trials. "That's a real priority for us," Van Bokkelen says. Now Athersys is reviewing clinical trial results with Chugai and the PMDA while continuing to pursue other clinical programs.

RepliCel and its Japanese partner Shishedo already have trials underway for RCH-01, a therapy to reverse pattern baldness in men and women. A year ago, Shishedo opened a cell manufacturing facility dedicated to R&D and the commercialization of RCH-01.

Hall says he envisions a straightforward path to commercialization in Japan because, "We're not using embryonic stem cells or conducting induced pluripotent stem cell therapy. We're addressing a deficit of fibroblasts or dermal cup cells." Cells are removed from the back of the scalp, isolated, replicated into the millions, and injected where needed, causing new hair follicles to grow.

"We can get more data faster in Japan, and then can license them [these products] in the West," Hall says. "Therefore, it's very attractive to go there."

Israel-based Pluristem also plans to enter the Japanese market with its placenta-based cell therapy PLacental eXpanded, or PLX. "We're hoping to announce a partnership with a Japanese pharmaceutical company this year and begin trials," Kleinhaus says.

"In Japan, we're targeting peripheral artery disease and critical limb ischemia. We conducted two Phase 1 trials in the U.S. and Germany, and we want to build on that for a Phase 2 or 2/3 in Japan. This could shave two to three years off time to market," Kleinhaus says. Importantly, she adds, "They're not expecting us to start from the beginning. We expect that Japan will accept cells manufactured outside the country for use in clinical studies conducted in Japan. We can scale up to produce 150,000 doses in our facility in Israel."

Mesoblast is reinvigorating its relationship with Japan's JCR Pharmaceuticals Co., Ltd. since the new regulations were passed. Last October, JCR filed a marketing approval application for Mesoblast's adult stem cell portfolio Prochymal (which Mesoblast acquired from Osiris Therapeutics). That therapeutic targets pediatric graft versus host disease (GvHD).

Also last fall, Mesoblast prioritized its lead candidates in Phase 2 trials for the Japanese market and is working with consultants in Japan as well as the PDMA to advance development and commercialization. The company is talking with potential Japanese partners.

Japan's new regulations regarding regenerative medicine are positive for the entire sector, so other companies are likely to explore their options in Japan, too. As Van Bokkelen says, "This will cause some companies to consider running trials in Japan or running truly international studies that include Japanese sites. It also creates the potential for a more efficient, less expensive path to market. That's something all investors should really like."

> *"Partnering interest from Japanese pharmaceutical companies is strong."*
>
> **KARINE KLEINHAUS, M.D., MPH**
> divisional VP for North America
> at Pluristem Therapeutics

SIMILAR U.S. PROVISIONS IN THE WORKS

Improvements in the U.S. regulatory system have included some provisions that are similar to those of the Japanese regulations. The Prescription Drug User Fee Act (PDUFA-V), for example, includes a new "breakthrough therapies" designation and broadens the potential application of the accelerated approval pathways.

Congress also is considering the 21st Century Cures Initiative. By taking a comprehensive look at the entire drug development process from discovery through development, commercialization, and delivery, Congress intends to find ways to streamline the process and bring life sciences products to market faster than is possible now.

"This is at the discussion draft stage and has bipartisan support," Van Bokkelen says. "I'm optimistic it will advance and will contain some important provisions to accomplish some of the same objectives as the Japanese legislation."

While U.S. efforts remain in discussions, Japan's efforts are in effect now. By granting conditional approval, Japan delivers a path to reimbursement while trials are underway, demonstrating a commitment to bringing advanced regenerative medicine to its populace and to enhancing its standing as a destination that actively supports biotech innovation.

Advice From A Serial Pharmaceutical Entrepreneur

DAN SCHELL Editorial Director

Twenty-two years after graduating college, Michael Jaharis purchased his first pharmaceutical company. That was in 1972. Four decades later he had amassed a career — and a fortune — in the pharmaceutical industry highlighted by the sales of three companies: Key Pharmaceuticals, Kos Pharmaceuticals, and Pearl Therapeutics.

Along the way he experienced plenty of the trials and tribulations that go hand in hand with being an entrepreneur. "When you run a company, you are always concerned about things such as raising capital, making payroll, or just how you're going to make everything work," Jaharis says. "We also asked ourselves, 'What do we do, or what can we do, to make people aware of at least one of our drugs?'" Through those struggles and by answering those tough questions, he was able to forge some best practices that stayed with him with each subsequent investment and challenge.

KEY PHARMACEUTICALS

When Jaharis and fellow investors purchased Key Pharmaceuticals in 1972, the company was essentially bankrupt. It could not compete with larger companies on multihundred-million-dollar discovery and development projects for new chemical entities (NCEs). "I realized the only way to create value for this small, bankrupt company was to examine its existing strengths. I saw Key's expertise in sustained-action formulations as a way to improve the effectiveness, and in some instances, the potency, of drugs that were already available at the time. So, we were able to cost-effectively commercialize a succession of products that addressed deficiencies in the original product while dramatically improving patient compliance. This was the kind of innovation that Key could afford, which is why I called this approach 'affordable innovation.'" Of course this specialty pharma approach is now well-established, but the idea was new and innovative in the 1970s.

One of Key's early successes was the asthma drug theophylline, which patients self-administered multiple times a day. Key scientists devised a sustained-release delivery mechanism that allowed once-daily dosing with equivalent effectiveness and lower toxicity. Later, dissatisfied with the effectiveness of his company's sustained-action nitroglycerin product, Jaharis directed development of the first transdermal, sustained-delivery nitroglycerine patch. Transdermal remains one of the most-researched alternative-delivery technologies in specialty pharma.

In 1986, Jaharis sold the company to Schering-Plough for $836 million.

KOS PHARMACEUTICALS

Two years later, in 1988, Jaharis founded Kos Pharmaceuticals, a developer of prescription products for the treatment of chronic cardiovascular, metabolic, and respiratory diseases. He considers his proudest achievement at Kos to be the creation of a market for Niaspan, a prescription drug that increased HDL (good cholesterol) and lowered LDL (bad cholesterol). At the time, that was a unique strategy — a differentiator for Kos — considering most Big Pharma companies were focused on strictly LDL therapies.

Niaspan is not an NCE (new chemical entity); it is a reformulation of a vitamin of the B complex. Thus, Kos did not spend money inventing the molecule, but instead, created a more patient-friendly formulation, which made it affordable for the small company to develop and bring the drug to market. "I once again applied the concept of affordable innovation and utilized drug delivery technology to develop and bring to market a high-performing cardiovascular product."

In 2006 Abbott Labs purchased Kos Pharmaceuticals for $4.2 billion.

PEARL THERAPEUTICS

Jaharis' venture capital firm Vatera Healthcare Partners invested in Pearl Therapeutics in 2010. Recognizing the firm's innovation in its respiratory products for COPD, Vatera funded clinical, regulatory, and business development efforts as well as provided financing to support new product development. Funding Pearl's programs into Phase 3 clinical trial testing validated the company's technology and paved the way to the sale to AstraZeneca for $1.15 billion in 2013. "Our experience with Pearl reinforced our belief in the value of having a strong scientific team and supporting innovative research," comments Jaharis.

Vatera continues to work with innovator companies working on treatments for serious, prevalent conditions for which existing treatments are ineffective or nonexistent. "I am excited about the projects we are involved in, not only from the investment side, but also because of the potential to fulfill an unmet need," says Jaharis.

FUTURE DRUG DISCOVERY OPPORTUNITIES

During its heyday, NCE discovery and development focused on a limited number of accessible biological targets and an equally circumscribed set of molecular

"Top managers should ask themselves if they are continuing to innovate."

MICHAEL JAHARIS

scaffolds. Innovation became more difficult as companies mined tried-and-true approaches to drug discovery. After a period of playing the law of big numbers with 100,000-molecule (and larger) compound libraries, new biological tools emerged that allowed for a more targeted approach to drug discovery and development. Yet the feeling persists that the golden age of small molecule drug discovery is fading; with the harvest of "low-hanging fruit" (i.e., well-known and high-patient-volume diseases such as hypertension that now have multiple small molecule treatment approaches), innovation in small molecule development is now a less attractive pharmaceutical target. Simultaneously, the maturation of specialty pharma has created serious financial entry barriers.

Jaharis acknowledges the differences between then and now, but remains highly optimistic about the future. Bringing a therapy to market is more difficult today than when he acquired Key. Evermore watchful regulators and the ballooning costs of drug development have been significant factors. The time and cost of discovery through development has been estimated at 10 years and $2 billion. Although these kinds of figures have been challenged, higher than ever development costs are now accepted as fact.

"I would say that the targets for pharmaceutical entrepreneurship have changed. Yes, conditions such as hypertension, cholesterol, asthma, and so on that affect large numbers of patients are now very well served through multiple pharmacological options. But, that doesn't mean there isn't room for improvements and enhancements," he says.

One area still ripe for innovative therapies is cancer. Many forms of the disease still lack safe, effective treatments that significantly prolong life. Jaharis also likes the prospects for drugs that fight diseases (including hepatitis C), treatment-naïve markets such as for celiac disease, and rare or orphan disorders.

Not every pharmaceutical entrepreneur will succeed to the extent of Michael Jaharis. Yet opportunities exist and continue to emerge as innovators seek to fulfill unmet medical needs. According to Jaharis, good business prospects begin with a passionate, knowledgeable management team with proven track records. From there, entrepreneurs should create a vision for their business that will attract funding as a start-up.

"I lean toward branded pharmaceutical products. While generics have a role in the pharmaceutical armamentarium, innovation creates more exciting opportunities because introducing new products directly improves people's lives," he says.

INNOVATION IS ALIVE AND WELL

Despite pricing, regulatory, and scientific challenges, Jaharis believes innovation in pharmaceuticals will continue. He stresses that keeping an entrepreneurial pharmaceutical company on the right path is a matter of making consistent progress toward goals. "Top managers should ask themselves if they are continuing to innovate, if their therapies are still relevant to patients, and if they are expending precious resources thoughtfully. And while it's important to stay focused on your original goals, you also need to be flexible enough to adapt to changing environments."

His last bit of advice is one echoed by top executives in all forms of business, but, considering his track record, it comes off less as a cliché and more like a dictum. "My strongest belief is that all success in business depends on a manager's ability to recruit good people who can work without significant monitoring. This becomes especially important when selecting people who work in areas in which a manager is not an expert." L

HOW MICHAEL JAHARIS GOT STARTED IN PHARMA

After graduation from Carroll University in 1950, Michael Jaharis was drafted and soon found himself in a medical unit in Austria where he helped run medical and pharmaceutical supply during the Korean War. Upon his discharge Jaharis decided to obtain his law degree, but he needed a job to cover tuition.

Based on his Army experience, Jaharis was hired as a sales representative for Miles Laboratories in its prescription drug division. "My territory extended from the north of Chicago's Loop to the Wisconsin border. At the same time I began law school at DePaul University as a night student. I'd planned on opening a law practice after graduation."

After receiving his JD, Jaharis moved to Miles' legal department. His mentor was John Buckley, who managed food and drug law for the Miles ethical and over-the-counter divisions. Jaharis credits Buckley with teaching him what was possible within the legal framework of a growing, dynamic industry. Jaharis eventually rose to top legal executive counsel for food and drug law at Miles and became involved in marketing as well. "We had a lot of good lawyers at Miles, but not many considered using the law to expand a drug portfolio," he says.

As a sales rep, Jaharis recognized that acetaminophen was as effective as aspirin without what he calls "unpleasant side effects." He recommended Miles explore the potential for acetaminophen as a standard tablet instead of as part of the Alka-Seltzer line as a "fizzy tablet." The company ignored Jaharis' advice. In the meantime, Johnson & Johnson bought a small company that was promoting the acetaminophen formulation Apamide, and ultimately introduced the drug as an OTC tablet that later became Tylenol – a brand that is arguably the most successful OTC medicine ever.

Deal Flow Prompts Companies To Understand New Revenue Recognition Standard

RYAN STARKES, PATRICK HUNNIUS, & JENNIFER FELDMAN

Whether you're ready or not, significant accounting changes are coming, and they aren't just a problem for your auditor. For life sciences companies considering a merger, acquisition, or strategic partnership in the near future, an understanding of the new standard for revenue recognition (i.e., what month earnings are reported on the financial statement) and its potential impact on deal structures will be critical.

A year ago, the Financial Accounting Standards Board (FASB) and the International Accounting Standards Board (IASB) (collectively, the Boards) announced a long-awaited new standard for revenue recognition that replaces existing U.S. generally accepted accounting principles (GAAP). The impact is likely to be far reaching, across all industries, and as a result, implementation questions are mounting. Indeed, the FASB is exploring a possible delay in the implementation date. Still, life science executives cannot afford to sit back and ignore the standard until final guidance is in place.

Revenue recognition in the life sciences industry is particularly complex, because companies typically have revenue streams not only from the direct sale of drugs or medical devices, but also from licensing and other arrangements from third parties who assist in the process of bringing products to market. How exactly the new standard will be applied to each revenue stream is a subject for another article, but it is important to note that previous guidance on certain forms of revenue are superseded by the new rules. Despite the breadth and significance of these changes, a recent poll by BDO of 200 CFOs found that over half had not yet familiarized themselves with the new standard.

This is not entirely surprising given that there are around 700 pages of guidance to sort through. However, companies will likely have an additional year to adopt the new rules as FASB recently proposed a delay in the effective date, pushing back the deadline to 2018 for public companies and 2019 for private companies. Meanwhile, other companies are in the process of planning for a full retrospective adoption. In addition, the FASB is continuing to refine the standard through formal amendments based on implementation issues raised by stakeholders, specifically regarding license arrangements. In other instances, the FASB's Transition Resource Group (TRG) may discuss an implementation issue and conclude that preparers can interpret the standard consistently with respect to that issue. When this occurs, the TRG may decide that further changes to the standard are not necessary. The discussion papers for these issues are available on the FASB's website and might be useful for life sciences companies that are analyzing the impact of the new revenue rules.

IMPACT ON REVENUE STREAMS

With the new standard fast approaching, life sciences companies should be proactive in considering the new standard and whether or how it affects their current revenue recognition analyses and policies. Specific sources of revenue for life sciences companies should be assessed in light of the new standard, such as licensing agreements, variable consideration, and reseller agreements.

- **Licensing of Intellectual Property:** Under the new standard, life sciences companies will need to determine whether a particular license provides a right of access or a right to use the underlying IP. If a license provides a right to use the company's IP, then the revenue is recognized at the point in time the license transfers to the customer. The Boards are developing guidance to make the access vs. use judgment easier for companies to apply.

- **Variable Consideration:** Under the new standard, companies may be able to recognize a portion of revenue from revenue streams such as bonuses and milestone payments *before* milestones are achieved, when the risk of failing to meet those milestones is low.

- **Reseller Agreements:** Under the new standard, companies might be able to recognize revenue when a product is transferred to the reseller once they have enough experience to estimate variable components of pricing such as returns and chargebacks.

IMPACT ON LIFE SCIENCES INDUSTRY DEALS

Life sciences companies continue to see a great deal of interest from investors, public markets, and strategic buyers. The hot IPO market has added new potential takeover targets to the mix, according to Bloomberg, and in the first month of the year there were five deals with headline values of $1 billion or more, according to PMLive. In March, AbbVie made headlines with a $21 billion deal to acquire

Pharmacyclics. With the market ripe for transactions, life science executives need to consider how the new standard can and should impact the deal structure.

Transaction values are typically predicated on the "potential" market (i.e., revenues) for products in development, and forecasting the timing of cash flows from related licenses and other arrangements, and the recognition of revenue is critical. The new revenue recognition standard brings potential changes to how revenue from each of these sources is recognized. Public life sciences companies are properly disclosing in 10-Qs and 10-Ks that they are aware of the new standard and are evaluating the potential impact, if any. The SEC expects that companies will be going through a more thorough review process over the next year to provide better guidance on the impact.

While a more thorough review of the new standard may be on the horizon for many life sciences companies, a transaction could force a company to expedite its analysis of several revenue recognition issues. For example, consider a transaction where a company agrees to pay royalties on future products. Traditionally, the language in this type of arrangement will reference revenues in accordance with U.S. GAAP. But if one party is treating revenue under legacy U.S. GAAP and the other is complying with the new standard, what "revenue" means could be very different to each company. For companies considering a deal in the coming months, the lack of clarity about implementation dates and potential changes in the standard, coupled with a transition period where some companies have adopted and some have not, is creating a host of challenges.

The new standard brings potentially wide-reaching changes for how life sciences companies recognize revenue and a resulting impact on deal structure. Companies should consider an assessment of how the standard will affect them and any corresponding changes in accounting policies or internal controls that may be required. Companies should also consider monitoring discussions of the SEC and the Boards on these changes. Looking at this proactively will allow companies to be in the best position possible when facing a potential industry deal amidst the changing standard.

Ryan Starkes is a partner and leader of the Life Sciences practice at BDO USA, LLP. Patrick Hunnius is a senior counsel and Jennifer Feldman is of Counsel in the Litigation practice group of DLA Piper.

How Leaders Can Promote Continuous Learning In Today's Organizations

TANVEER NASEER, MSC.

When it comes to effectively leading organizations in today's 24/7 global economy, it's clear that the days of command-and-control leadership are well behind us. Instead, what's needed are leaders who promote a continuous learning environment where employees can grow, evolve, and do work that matters. Fortunately, it doesn't take much for us to create such conditions in our workplace. To begin the process in your organization, here are three tactics you should employ:

1 ENCOURAGE YOUR EMPLOYEES TO CHALLENGE THEIR ASSUMPTIONS

When our brain performs tasks or makes decisions, it creates waste by-products such as beta-amyloid and other metabolites, which can reduce our brain's ability to concentrate and efficiently perform tasks.

Given how we have a limited daily reserve of energy at our disposal, our brain tends to protect us from using it too much by employing shortcuts in the form of habits, where we perform these tasks with minimal thought or effort. Unfortunately, this also leads to us making assumptions of what can be done or even whether something is worth pursuing.

As such, if we are to ensure our organization remains adaptive to external changes — as well as to promote our ability to innovate — we need to ensure our employees are challenging their assumptions of what's possible so we might discover improvements and new opportunities for our organization.

2 PROVIDE AN ENVIRONMENT WHERE EMPLOYEES FEEL SAFE TO FAIL

One thing we're all hardwired to do is to pay more attention to the things we perceive as being negative. As a protective measure, this neurological mechanism makes a lot of sense in how it helps to keep us out of harm's way.

Unfortunately, it's this same neurological mechanism that causes many of us to avoid failure because we've trained our brain to view failure as a negative outcome. And naturally, when we're focused more on avoiding failure, it's harder for us to be more open to learning.

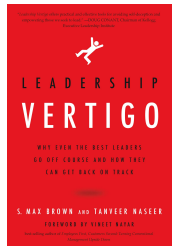
That's why it's important that we help our employees to shift their focus away from avoiding failure to learning why certain approaches are inefficient and how we might do things better going forward.

3 PROMOTE LEARNING AS A SHARED EXPERIENCE

One of the core psychological needs that research has shown we all share is relatedness — where we feel a connection, a bond, and a sense of commonality with those around us. By fostering an environment where our employees share what they've learned, we can use these moments to strengthen the sense of community and belonging that will help them continue to look for ways for us to do better than we do today.

By creating a continuous learning environment in our organization, we can inspire our employees to believe in the vision that defines the organization because they know they will acquire the skills and experiences to help make it a reality.

Tanveer Naseer is an award-winning, internationally-acclaimed leadership writer, keynote speaker, and author of *Leadership Vertigo*. Read more of his writings on leadership and management on his leadership blog at TanveerNaseer.com.



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