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AstraZeneca Eliminates Capacity Guesswork

Andrew Skibo Regional VP of Supply Biologics, Global Engineering, and Real Estate, applies a risk-based approach to capacity planning **p. 24**

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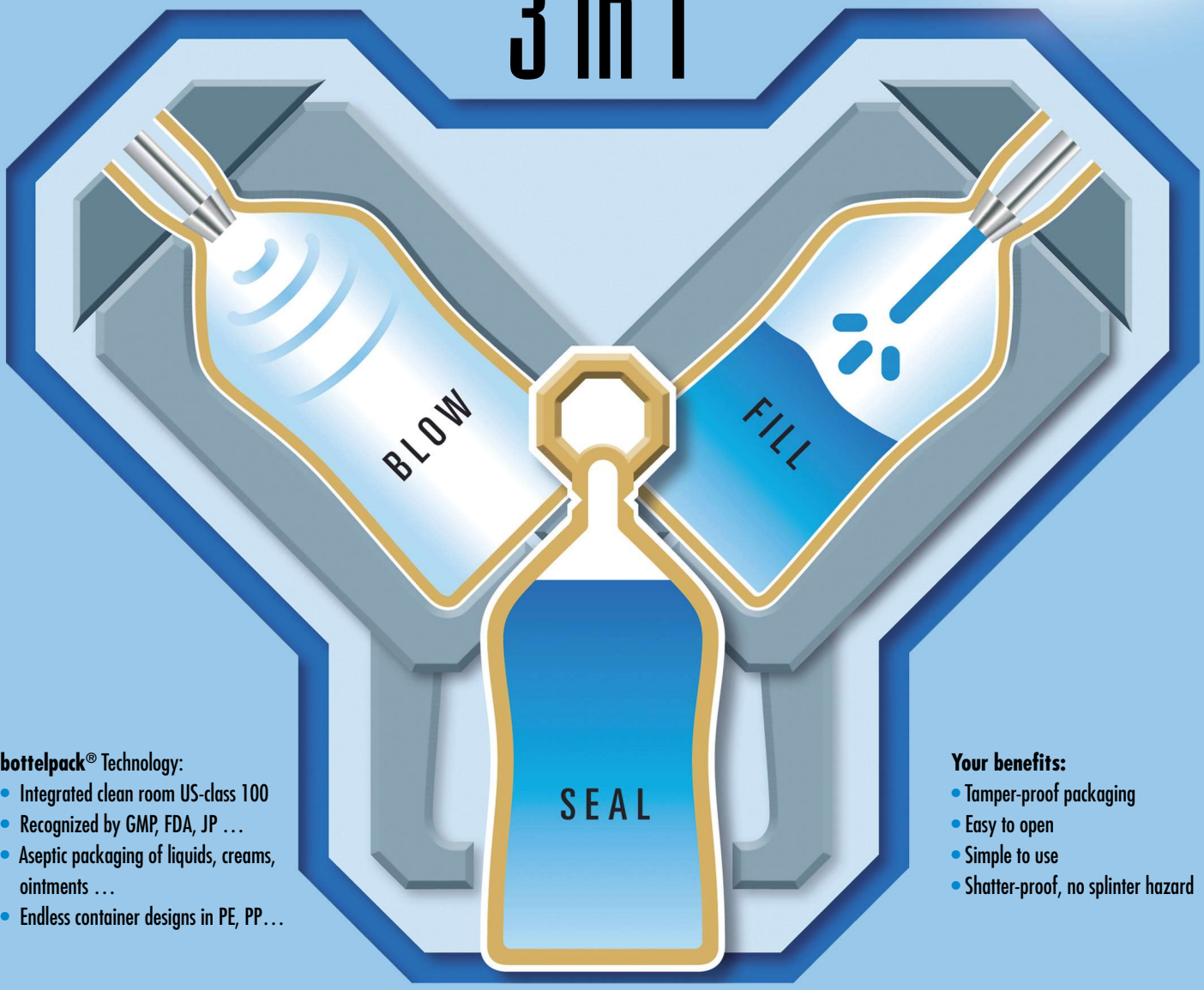

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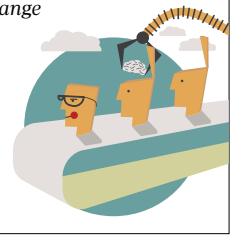

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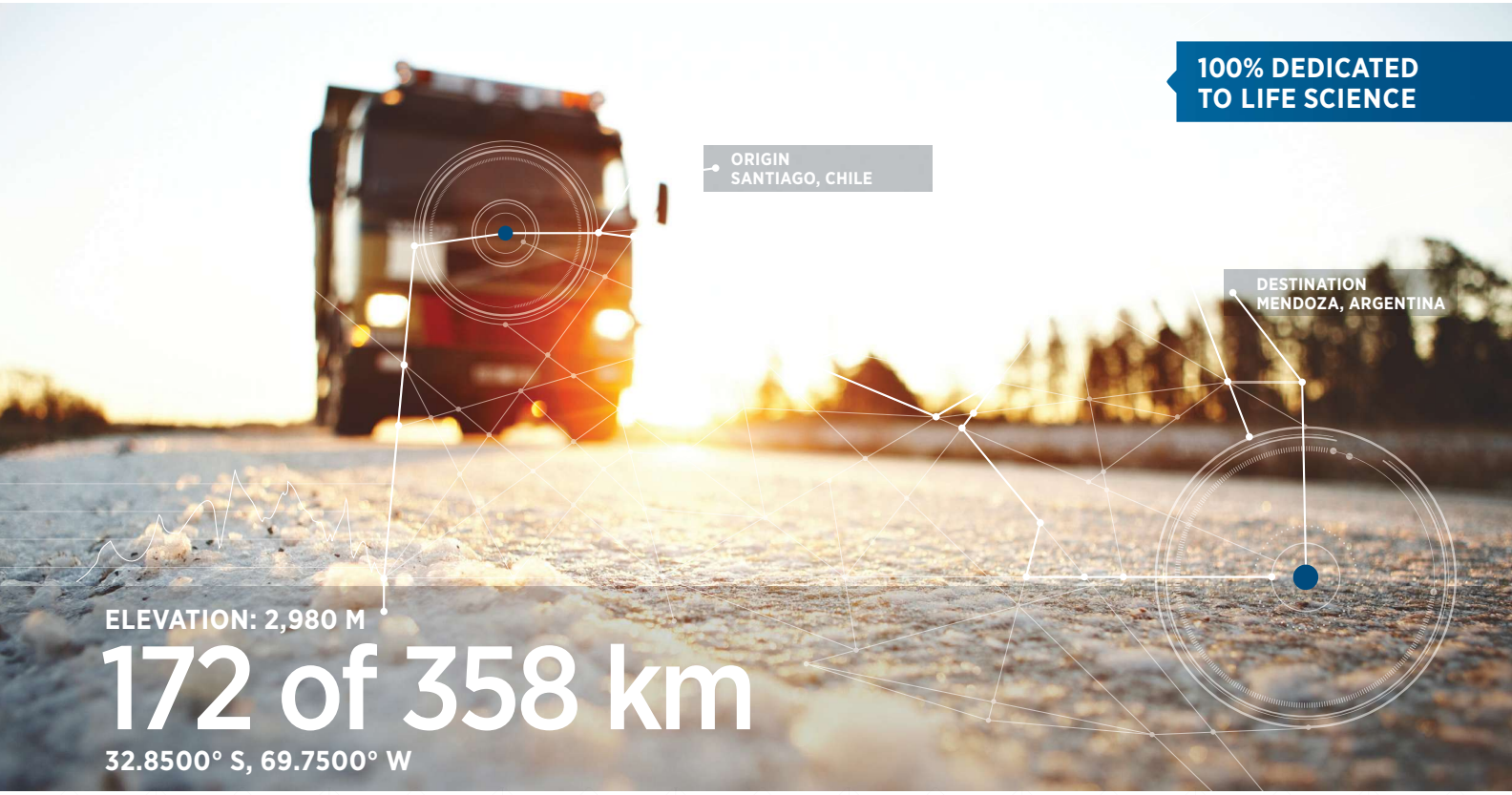

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It's Not The Tool, It's The Technician

ROB WRIGHT Chief Editor

My son plays on his college's golf team. In the fall he was struggling with his putting. What is the obvious solution needed to fix the problem? Why, to buy a new putter of course. It could not possibly be anything to do with the technique. It must be the tool. Many of you who are golfers are smiling as you read this because you know you have taken the same approach in trying to improve your game. However, you don't have to be a golfer to understand this concept, and it certainly doesn't apply to just your hobbies. "Show me a cool tool; let's go buy a model and it will tell us the right answer," says biologics manufacturing veteran, Andrew Skibo, who sat down with me to explain the nuances of applying a risk-based approach to plan for biologics manufacturing in this month's feature article on page 24. Taken out of context, you would think, "Ah, Skibo must be a golfer." But the regional VP of supply biologics, global engineering, and real estate at AstraZeneca (AZ), whose hobby of choice is actually sailing, was being facetious. He soon clarified the statement with the following words of wisdom, "If you don't first understand how the plant runs, you shouldn't touch the model." In other words, before you throw people or products at a problem or an opportunity, seek first to understand the process.

There is little doubt that the technology and tools of today, such as software, computers, or even golf clubs, are significantly superior to those of just a few years ago. Though all hold the potential to dramatically improve performance, more often than not, they fall woefully short achieving the anticipated ROI. Why? Well frequently, it is the result of our being so busy trying to complete various tasks that we don't slow down long enough to think about how to best approach a problem or capture an opportunity. For example, many golfers have dropped a few hundred dollars on the latest, greatest, humongous-headed driver thinking this will straighten out their shots off the tee. The research employed was a sample size (n = 1), as in, they tried a friend's club on just one shot and hit it straight and true, failing to consider the possibility of the halo effect being at play. Instead of seeking a quick fix, slow down to determine a better long-term solution and apply a measured approach to its implementation.

When Skibo and his team began change management at the Frederick plant, they decided to take the foot off the accelerator and be more measured in implementation. Though in theory, all of the changes could have been made in four months, Skibo and his team felt this would have increased risk and stress. "I want the running of this plant to feel like deep breathing, calm and collected, not like a bunch of ants running around because the hill just got kicked over," he analogizes.

As for tools that can improve you as a technician, Skibo has a few simple ones, such as the Myers-Briggs Type Indicator (MBTI) personality test. Though it is very common and fundamental, he admits to using MBTI extensively. The better you understand how your team thinks, the better able you will be to communicate and gain buy-in. Another tool he recommends is even more fundamental — the telephone, along with the knowledge to use it. "You can learn a lot by interfacing with your peers," he testifies. My son agrees. For instead of taking the quick fix, he asked one of the best putters on the team for help on fixing the technician and not the tool.

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Q What Is The Best Leadership Advice You Ever Received?

A "Full speed ahead, and damn the torpedoes!" is a popular phrase characteristic of Dr. Phil Russell's leadership style, who is now a retired Army three-star general. Phil was a mentor during my nearly two-decade tenure at the Walter Reed Army Institute of Research. He wasn't afraid to make hard decisions, especially when timing was critical, and not all the data was available to assess every option. His point was that someone needs to lead, and there is never enough data to make a truly informed decision, especially by a committee. So you make the best decision based on available data, move ahead, and take responsibility for the consequences. Taking personal responsibility for the decisions we collectively make is what being the CEO is all about.

CAROL NACY, PH.D.
Dr. Nacy is CEO of Sequella, Inc., a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed. Prior to her business experience, she directed research in tropical infectious diseases at Walter Reed Army Institute of Research, Washington, D.C.

A Early in my career I was asked to lead a multidisciplinary task force to address broad strategic challenges that negatively impact productivity during drug development. This required me to move out of my comfort zone into the proverbial "third room" of life experiences. While building my team, my boss and mentor said, "Remember, you don't have all the answers, and neither do I." That advice had a profound impact on how I chose my team – a team with diverse experiences and expertise that would come together to achieve things no single perspective could possibly achieve. It helped me recall an experiment that illustrated the power of diversity in solving complex problems. In that study, a group of exceptionally bright individuals with similar life experiences lost out to a group with more modest intellectual firepower but that had very diverse backgrounds and perspectives.

JOHN ORLOFF, M.D.
Dr. Orloff is the head of global clinical development for Merck Serono. Previously, he served as chief medical officer and senior VP of global clinical development at Novartis Pharmaceuticals.

A About 30 years ago a friend of mine, Mike Duffy, presented me with a small, framed copy of an inspirational poem called "The Man in the Glass." It sat on my desk for years collecting dust and the occasional glance. Eventually, I memorized it and have repeated it to myself many times over the years. Mike started out in his father's small, Iowa-based business right out of school and worked his way through the company to the role of President/CEO. The company is now the multimillion dollar Per Mar Security Services and is still headquartered in Davenport, IA. His golden rule philosophy, underscored by his Midwest sensibilities (a man so humble he doesn't even put his title on his business card), has elevated him to the highest levels of success and respect within his company, personal life, and community.

KEVIN O'DONNELL
Mr. O'Donnell is senior partner at Exelsius Cold Chain Management Consultancy U.S., an international provider of consultative, research, and training services to manufacturers, airlines, forwarders, and other stakeholders in the life science logistics sector.

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The Looming Battle Between The Pharmaceutical And Health Plan Industries

JOHN McMANUS The McManus Group

Although generic utilization has never been higher — a new report by the IMS Institute for Healthcare Informatics notes that 86 percent of all prescriptions filled were generic and more than half of prescriptions cost patients on average less than $5 out-of-pocket — the growing cost of specialty medicines is sparking a marketing and policy battle between the pharmaceutical industry and plans that cover those drugs.

That same report found that just 2.3 percent of prescriptions accounted for 30 percent of all out-of-pocket costs, including 17 drugs that were launched last year for orphan diseases with small populations of patients (less than 200,000). Specialty medicine costs grew by 14 percent last year and are projected to climb 63 percent by the end of 2016, in part because of breakthrough treatments for Hepatitis C, a disease that affects 3.4 million patients.

Express Scripts, a pharmacy benefit manager that processes more than 1 billion U.S. prescriptions annually, urged its insurance and employer clients to join a coalition to stop prescribing Sovaldi, a breakthrough for Hepatitis C, once competitor products hit the market unless the sponsor company, Gilead, lowers its price. Merck, AbbVie, and Bristol-Myers Squibb are currently in clinical trials in the therapeutic space, but their pricing decisions remain unclear at this time. Steven Miller, Express Scripts' chief medical officer, said, "What they have done with this particular drug will break this country."

Break this country? Sounds like hyperbole. However, that perspective may be understandable from an entity whose sole job is managing one silo of healthcare spending with no appreciation or recognition of the enormous savings that drugs can deliver to overall medical costs or health outcomes. Hepatitis C infections kill 15,000 patients a year and are a leading cause of liver transplants, according to the Centers for Disease Control and Prevention. A liver transplant costs $175,000 or more, twice the cost of a Sovaldi regimen.

Hepatitis C is a smoldering disease with symptoms that are often not recognized for decades but can cause liver damage, cirrhosis, and liver cancer, which often requires a liver transplant or results in death. The disease is particularly prevalent in Baby Boomers, comprising 75 percent of Hepatitis C infections, of which one million will qualify for Medicare in the next 10 years. Sovaldi proponents note that it is comparably priced to the now-obsolete regimen of a dozen-pills-a-day-plus interferon that has a lower cure rate (75 percent vs. Sovaldi's 90 percent) as well as poor adherence because of the miserable side-effects of interferon injections that inflict flu-like symptoms during the months of treatment.

But that's not deterred the nemesis of the brand-name pharmaceutical industry, Energy & Commerce Committee ranking member Henry Waxman (D-CA) and his Democratic colleagues on the committee, from issuing a sternly worded letter to the CEO of Gilead demanding he justify the cost of the $84,000 treatment. While the retiring Waxman lacks the clout he once had, that letter sent the entire biotech sector's market value plummeting upon its release. Investor unease about possible price controls or pressure to restrict access sent many out of the stocks, believing their steady upward climb might be a bubble waiting to burst.

Express Scripts' treatment of Sovaldi is typical of a trend toward noncoverage, which now includes a list of 44 drugs, such as Novo Nordisk's two top drugs, Victoza and Novolog, and Pfizer's Xeljanz. CVS Caremark, a major competitor to Express Scripts, also blocked treatment to 34 therapies last year and intends to expand the list. Molina, the largest Medicaid managed care plan, is trying to reserve coverage of Sovaldi and other specialty pharmaceuticals for only its sickest patients.

The battle over these products has spilled into policy debates in Washington. Health plans and PBMs (pharmacy benefit managers) were behind an effort to encourage CMS (Centers for Medicare and Medicaid Services) to eliminate access protections to three of the six protected classes — antipsychotics, antidepressants, and immunosuppressives — arguing that covering substantially all drugs in those therapeutic classes was costing Medicare $4.2 billion. A fusillade counter by patient groups, pharmaceutical companies, and other stakeholders forced CMS to withdraw that proposal in its entirety.

Plans also attempted to eliminate the science-based U.S. Pharmacopeial Convention from its role in defining therapeutic classes for purposes of establishing "Essential Health Benefits" in Obamacare plans, preferring those classes to be determined by the plans

"For years the pharma industry has been accused of producing too many 'me-too' drugs."

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themselves. That proposal was rejected by Health and Human Services. But plans succeeded in limiting coverage requirements to one drug per class, unlike Medicare Part D's standard of two drugs per class, much to the pharmaceutical industry's chagrin.

Meanwhile, the chatter in Washington is that America's Health Insurance Plans (AHIP), having successfully beat back pending cuts to the Medicare Advantage program, is now focusing on specialty product cost challenges to its Medicare and Medicaid plan members. Some plans are asserting they cannot absorb the cost of specialty products like Sovaldi because rates were established before the drug was launched.

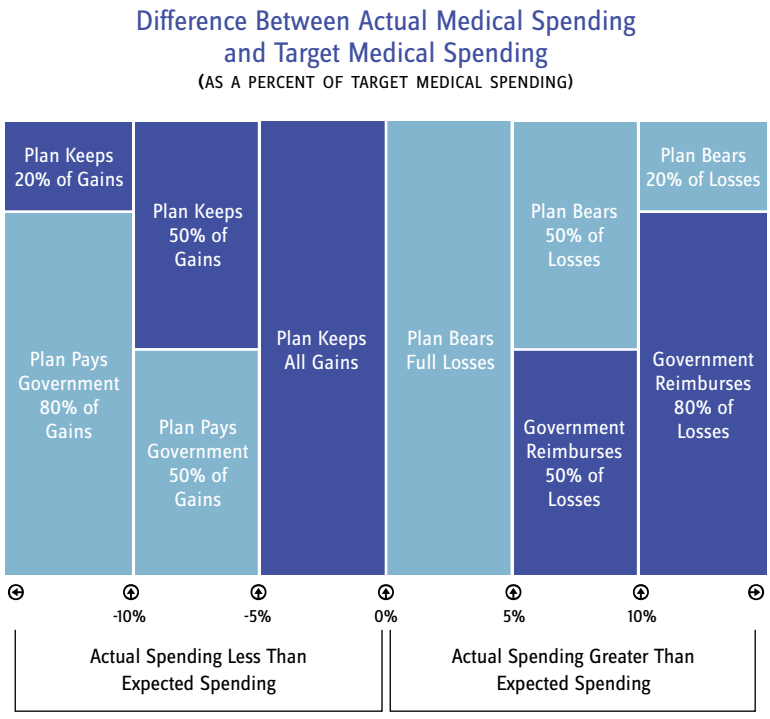
In actuality, Medicare Part D is well equipped to absorb the costs and fundamentally protect the plans through the automatic stabilizers built into the program. The plans are responsible for only 15 percent of the costs an individual beneficiary consumes above the catastrophic threshold, with the federal government paying 80 percent in reinsurance and the remaining 5 percent as co-insurance by the beneficiary. In addition, plans are protected for aggregate expenditures that exceed target costs through "risk corridors." Under the risk corridor program, Medicare reimburses plans for 50 percent of losses between 5 percent and 10 percent of the target and 80 percent of losses above 10 percent of the target. The mirror image applies as well for profits that exceed the target.

Historically, risk corridors have required plans to pay back excessive profits instead of being insulated from excessive costs. The 2013 Medicare Trustees Report documented net risk-sharing payments of $900 million for the 2011 plan year, $700 million in net payments for the 2012 plan year, and $1 billion for the 2013 plan year. In other words, plans have ample latitude to absorb additional costs.

CMS possesses the authority to increase risk-adjusted payments to plans for certain medical indices, which could be an area pharmaceuticals and plans could collaborate to enhance. But those payments are based on claims data, which means that there would be a 2- to 3-year time lag until these higher payments could be realized.

For years the pharma industry has been accused of producing too many "me-too" drugs. "But the industry's success in producing innovative products that address unmet medical needs is raising the ire of certain payers that are tasked with controlling pharmaceutical spend but are not accountable to overall medical spend or health outcomes." After a relative period of détente between the pharmaceutical and health plan sectors, a lobbying battle between these two titans could become more intense.

Medicare Part D Risk Corridors



Source: The McManus Group

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

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WAYNE KOBERSTEIN Executive Editor

SNAPSHOT

With an industry-experienced management team and strategy, Savant Health Wellness & Prevention (HWP) is developing a novel anti-addiction medicine, an antagonist to a nicotinic receptor prevalent in the brain's reward centers that indirectly affects dopamine regulation. Dopamine disregulation is one definition of addiction, and the potential blockbuster may help break the vicious cycle of addiction, recovery, loss of tolerance, and relapse, often leading to fatal overdose. Savant is also developing a drug for Leishmaniasis in emerging markets and for travelers, and another for Chagas disease in the U.S. human and veterinary markets.

WHAT'S AT STAKE

When you find a vein of silver, follow it. In this case, silver stands for knowledge, as opposed to metals for investment and profit.

Since the JP Morgan Healthcare conference in January, where I first met Savant's CEO Stephen Hurst, I have been encountering a rich vein of companies that have one trait in common: They started first with the resolve to build a business and only later decided what they wanted in their product portfolios. For many reasons, I believe they have a lot to teach the predominant, product-first crowd of start-ups in the life sciences industry — the same ones that often ignore essential business principles and models in their haste to "Build it and they will come."

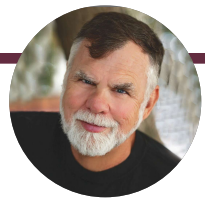
"You take a group of experienced biopharmaceutical executives who have been responsible for key areas of product development and get them in a conversation about what we would do if we had the opportunity to take all of our lessons learned and do something different. That's how Savant HWP started," says Hurst.

The groundwork-laying conversation for Savant included co-founders Scott Freeman, chairman and CMO, who had guided clinical development Nexavar (sorafenib) at Onyx, and synthetic organic chemist Martin Kuehne, as well as EVP Terence Boardman and SVP Jeanne Bonelle, former Hurst colleagues at InHale Therapeutics, now a Savant partner. Hurst's industry background is in partnering and business development.

In particular, Hurst says, the conversation began with the question, "What are the things that we don't want to do with our business?" The answers set the stage: "We don't want to be the little guy competing with a $60-billion Big Pharma. We don't want to work in areas where a lot of others are already working but in areas with significant unmet medical needs." And, in a somewhat unusual tack for a new company: "We would prefer to fail early and cheap rather than late and expensive."

Hurst says the latter principle stems from a basic lesson drawn from industry experience. "It is a business where you fail much more often than you succeed. The only adage that I've ever adopted from Jack Welch is, 'The single biggest obstacle to success is an inability to accept reality.'" Savant also avoided being disease-specific. "We wanted to be disease agnostic. Companies fall in love with their own technologies and will beat that dead horse to the nth degree, well beyond its useful life." Indeed, just before press time, reality ruled once again: A mid-April FDA hearing on Savant's lead program may force the company to restart the Phase 1 program for its anti-addiction drug.

By the criteria Savant had set for itself, it searched for opportunities and eventually chose one with large-market potential and two others aimed at emerging- and special-market needs. In principle, the company is free to roam into any therapeutic area, drugs, or devices, to fit its HWP mission and identity. The Master Lesson: Even if you do start a company with a product idea, build an experience-based business plan, define your do's and don'ts, plan for failures, and keep your options open. Another: Study companies like Savant to keep mining the silver vein.



STEPHEN L. HURST J.D.
Founder, Director, President, & CEO

Vital Statistics

5
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Headquarters
San Carlos, CA

Finances

Ownership –
Founders, Friends & Family, Employees

Total
$7.1M
expended to date

Founders
$750,000
invested

Friends & Family
$235,000
invested

Grant Revenue
$6.2M
to date

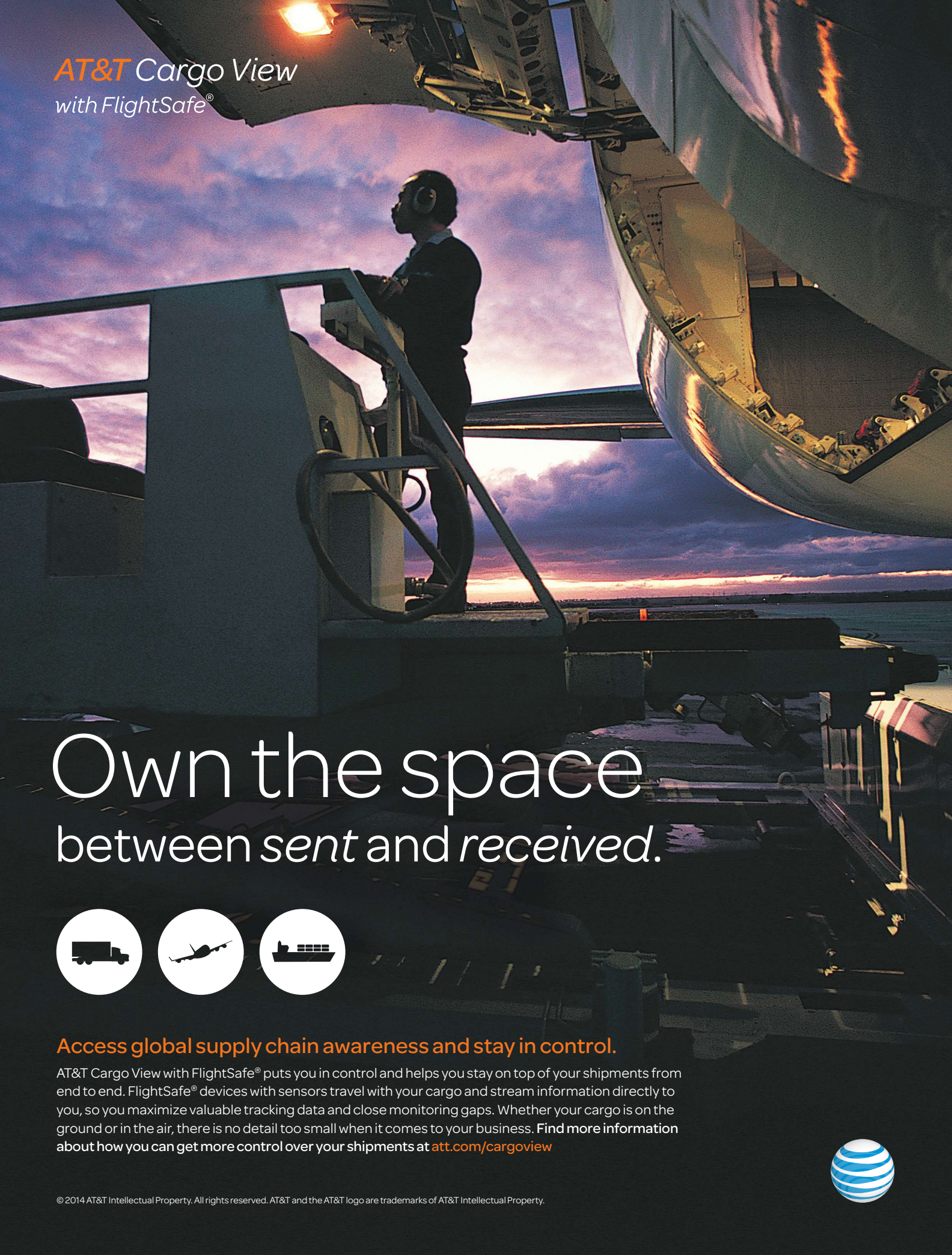
Research Partnership Funding

National Institute on Drug Abuse
$6.8M

Latest Updates

Filed U.S. Investigational New Drug (IND) for anti-addiction drug for the treatment of substance use disorders on February 7, 2014;

First-in-human dosing of anti-addiction drug expected mid-year 2014.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Can CROs Help Reduce The Expense Of Clinical Trials?

Figures reported by the Tufts Center for the Study of Drug Development state that the average capitalized cost of bringing a new drug to market is about $1.3B. Compare that to the 1991 cost of $318M, and after adjusting the amount for general inflation, it shows a 260% increase over the course of two decades in the cost of developing a drug. Industry data relays that the bulk of drug development costs are incurred during clinical trials, often, Phase 3 trials.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

> *"Partnering with a discovery-phase CRO with high scores in productivity and innovation can add value and reduce costs in early development."*

Increased costs make sense when viewed alongside the increase in the average length of a clinical trial (up 70 percent), and the average number of routine procedures per trial (up 65 percent), and the average clinical trial staff work burden (up 67 percent). Despite sharply rising costs, it is highly unlikely we will see a decline in clinical research.

In fact, in the past three years of Nice Insight research, the data has shown an increase in outsourcing clinical trials from 28 percent of respondents in 2012 to 41 percent in 2014. Big Pharma has the highest rate of outsourcing clinical trials at 46 percent, and emerging pharma showed the lowest incidence at 36 percent. These increases coincide with a sharp uptick in the number of registered studies on clinicaltrials.gov — 139,004 in 2012 and 164,703 as of April 8, 2014. As more biopharmaceutical companies emerge with the goal of developing new medicines, and each potential drug requires extensive clinical testing, these are numbers that will continue to grow rapidly.

Considering the majority of these clinical trials will be outsourced to CROs, are there ways CROs can help reduce the cost of bringing a new medicine to market? Definitely. In the early stages of drug development, a good CRO can help to improve preclinical throughput. As hypothesized in *Approaches to Assessing Drug Safety in the Discovery Phase*, an estimated 10 percent improvement in predicting failure before the initiation of clinical trials could save upwards of $100M in the costs associated with drug development. Partnering with a discovery-phase CRO with high scores in productivity and innovation can add value and reduce costs in early development.

INCREASING EFFICIENCIES TO REDUCE COSTS

A key area in clinical trial monitoring that has been encouraged by regulatory authorities, but has yet to be widely adopted, is risk-based monitoring (RBM).

Partnering with a CRO that specializes in RBM can ensure a strategy in which the efficiencies over traditional monitoring provide a financial break. An experienced CRO will be able to assist in identifying and defining the risks associated with the study and be able to implement the appropriate risk-management strategy. A clinical phase CRO with therapeutic experience relevant to the study and solid scores in quality will help to ensure a smooth transition to risk-based moni-

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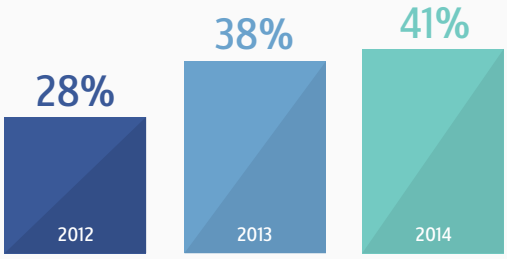
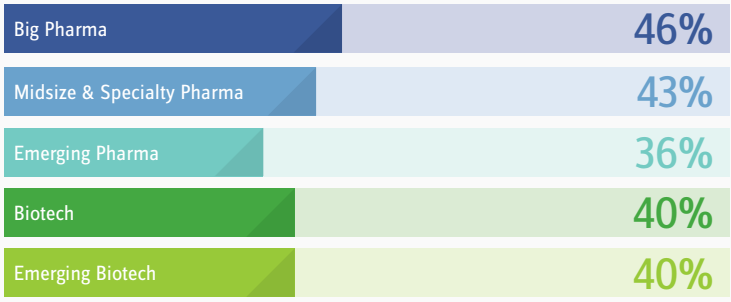
The Percentage of Respondents Who Outsource Clinical Research



The Percentage Who Outsource Clinical Research by Buyer Group



Changes in Clinical Trials: Resources, Length, and Participation*

Average length of clinical trial days	1999	460	
	2005	780	70%
Average procedures per trial protocol	1999	96	
	2005	158	65%
Average clinical trial staff work burden, work-effort units protocol	1999	21	
	2005	35	67%

***Source:** Tufts Center for the Study of Drug Development, Impact Report 10, No. 1 (2008)

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2013-2014 report includes responses from 2,337 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 100+ CMOs and top 50+ 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.

"Technology plays an important role in risk-based monitoring ... and can present an opportunity for reducing errors and expediting results."

toring where resources can be effectively prioritized without compromising the integrity of the study.

Technology plays an important role in risk-based monitoring regarding remote data capture and clinical trial monitoring systems that help to monitor specific sets of data for source-document verification. Technology can also present an opportunity for reducing errors and expediting results through electronic data collection. Electronic data collection can also reduce costs by decreasing set-up time for new studies because the standards will have been established during the initial software set-up. Nice Insight research has shown CROs that offer data management services score above the benchmark for regulatory and productivity, in addition to being perceived as more affordable. These are just some of the ways forming strategic partnerships with innovative CROs can add value beyond reducing internal fixed costs — the right CRO can help decrease the cost of bringing a new drug to market.

N. WALKER

S.FAZZOLARI

If you want to learn more about the report or about how to participate, please contact Nigel Walker, managing director, or Salvatore Fazzolari, director of client services, at Nice Insight by sending an email to niceinsight.survey@thatsnice.com.

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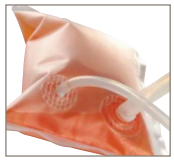

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Quality Management: How Much Are Vendors To Blame?

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

If you want to learn more about the report, please go to **bioplanassociates.com**

Biopharmaceutical manufacturing is one of the most demanding industries on its suppliers: demanding that its vendors be prequalified as primary or secondary, requiring confirmations of product provenance, certificates of analysis, and other sometimes onerous documentation. All of this is done for drug product quality and consistency. So it comes as no surprise that quality managers are continuing to take a close look at their vendors. Our 11th annual biopharmaceutical manufacturing industry report indicates that companies are vetting suppliers more closely than ever, demanding even higher levels of GMP/GLP compliance (see: "Who's Improving Bioprocessing in 2014?" in our January 2014 issue). In our current industry study — *11th Annual Report and Survey of Biopharmaceutical Manufacturers* — we review quality problems attributed to vendors, finding that half of our biopharmaceutical company participants complain of a variety of problems initiated by their vendors, from change notification problems, where they didn't notify clients of changes, to regulatory inexperience.

> *"The vast majority of industry decision makers attribute at least some quality problems to their vendors."*

8 IN 10 SUPPLIERS HAVE CREATED QUALITY PROBLEMS

Results from the study indicate that the vast majority of industry decision makers attribute at least some quality problems to their vendors. Overall, only 18 percent of respondents said that vendors have not created quality problems for them and that they are generally satisfied with their vendors in this regard.

The most common complaint in this highly regulated environment relates to suppliers not informing customers of changes, with half of the respondents frustrated by the problems suppliers create in this regard. In addition, 43 percent of respondents note that, overall, vendor change control is poor.

The high rate of problems due to poor vendor change control and poor product quality are troublesome because these factors potentially lead to batch failures and/or regulatory compliance issues for the biopharmaceutical manufacturer. It is, therefore, critical for manufacturers to develop stronger relationships with their vendors and to maintain quality agreements with specific requirements.

Clearly, change control is a quality problem plaguing the industry, but there are other issues, too (see figure 1). Other complaints cited by at least one-quarter of the industry include include poor service quality and poor product quality.

SIGNS OF VENDOR IMPROVEMENT

There are reasons to believe that vendors are improving, though. For example, the 18 percent of respondents this year saying they have not experienced any quality problems traced to vendors is a step up from nearly 16 percent last year. And on some of the quality issues identified, fewer participants are seeing problems this year.

That's particularly the case when it comes to the inadequacy of certificates of analysis for products. This year, fewer than one in five said that vendors had created problems for them in this area, down from roughly one-quarter of participants in the prior three years of surveys and roughly one-third of respondents in the three years prior to that.

Also this year, just 7 percent complained of vendors not filing a Device Master File

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on their product. That marks a new low for this issue, which has remained above 10 percent during most of the previous six years of surveys.

SERVICE PROBLEMS NOW OUTWEIGH QUALITY ISSUES

Interestingly, issues of product and service quality are moving in opposite directions this year. In a reversal of trends we observed in recent years, our latest report shows that vendors may be getting better at *producing* their products and services, but getting worse in *delivering* their products and services.

This year, 28 percent of respondents identified poor product quality as causing problems, down from 39 percent last year. In fact, this year's results are a sizable improvement from years past, in which as many as 45 percent of participants had cited product quality problems.

Instead, for the first time, we found more respondents complaining of poor quality service (29 percent) than poor quality products (28 percent). The uptick in service complaints came from about one-quarter of participants noting service quality problems in each of the past two years.

VENDORS STILL OVERPROMISE

Over a third (38 percent) of biomanufacturers are concerned that vendors continue to make promises they can't keep. And while this problem isn't unique to the biopharma industry, it becomes far more critical because the FDA and EMA are involved. Biopharma companies realize that their reputations and even their existence could be undone if suppliers don't provide what they say. This figure has hovered around this level each year since 2008. So the problem seems to be somewhat ingrained.

When vendors — particularly sales reps — make promises they or their companies cannot keep (and/or provide defective or inadequate products), it can be presumed that their customers will seek out other vendors with better, more documented products and better follow-through. However, qualifying a new vendor can be arduous, and most companies prefer to avoid switching.

To some extent, when vendors don't meet their promises, it may be due to vendor-customer communication problems and customers not "hearing" negative information concerning their purchase. Also, end users may not be asking the right questions or requesting all the available documentation regarding their bioprocessing equipment, materials, and supply chain — and vendors may not be routinely providing this info.

Also, end users may not be asking the right questions or requesting all the documentation available regarding bioprocessing equipment and their materials manufacturing and supply chain, and/or vendors are not providing it.

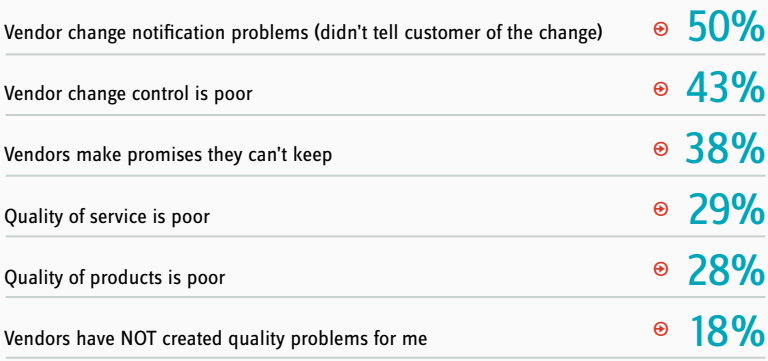
QUALITY AGREEMENTS ARE CRITICAL

One of the challenges faced by biopharmaceutical manufacturers is that, due to regulatory demands, it is often difficult to change vendors for key materials. For this reason, manufacturers must continue relationships with vendors even when there is a high degree of dissatisfaction with various aspects of the material or service provided.

In order for manufacturers to build confidence in their relationships, they must have solid quality agreements with suppliers and perform regular audits to be certain that both parties have a clear understanding of exactly what is expected. One of the biggest issues with vendors is managing their own unanticipated manufacturing changes. Vendors' raw materials suppliers may not be communicating up the chain in a timely way to either the manufacturer or the equipment users. In some cases, vendors do not realize that a change has been made by *their* supplier until long after the fact. This creates problems that some attribute to lack of communication. Solid quality agreements can help reduce these problems for client companies and build confidence into their relationships.

FIGURE 1

Selected Areas Where Suppliers have Created Problems



Source: 11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2014, BioPlan Associates, Inc.

Survey Methodology: The BioPlan annual survey of biopharmaceutical manufacturers yields a composite view and trend analysis from over 300 responsible individuals at biopharmaceutical manufacturers and CMOs in 29 countries. The survey included over 150 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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ASTRAZENECA'S BIOLOGICS VETERAN APPLYING A RISK-BASED APPROACH TO PLAN FOR CAPACITY

ROB WRIGHT Chief Editor

IMAGINE YOU ARE SEATED AT A TABLE preparing to discuss the manufacturing of biologics. The person across from you possesses nearly 40 years' worth of wisdom on the topic. You, on the other hand, have zero experience in this field. Kind of like a rookie stepping into the batter's box against Nolan Ryan and understanding that if a 95 mph baseball is coming at his head he has less than .4 seconds to get out of the way.

ANDREW SKIBO Regional VP Of Supply Biologics, Global Engineering, And Real Estate At AstraZeneca (AZ)

Photos by Caruso Studio

ASTRAZENECA'S BIOLOGICS VETERAN – APPLYING A RISK-BASED APPROACH TO PLAN FOR CAPACITY | By R. Wright

When I recently sat down with Andrew Skibo, regional VP of supply biologics, global engineering, and real estate at AstraZeneca (AZ), I was the guy with no experience. Sure, I have 20+ years of pharmaceutical industry experience, but after a few minutes of conversation, I learned that this exchange could only be described as one between a veteran and a rookie — and I was the latter.

Skibo has an impressive list of industry accomplishments, including overseeing large-scale capital projects that garnered two International Society for Pharmaceutical Engineering (ISPE) facility of the year awards (FOYA) and two Leadership in Energy & Environmental Design (LEED) Gold awards. But what you can't conclude from someone's CV is the skill with which they are able to communicate their wisdom. For instance, I found Skibo to be a patient and skilled communicator, putting me at ease by stating, "If I answer any of these questions in too much detail, stop and fine-tune me as to the level you need." What follows are his insights on applying a risk-based approach to modeling and planning for biologics manufacturing capacity. Of course, he knows a thing or two about this topic, considering nearly half of AstraZeneca's 2014 development pipeline falls into the large molecule (biologic) category.

PLANNING FOR BIOLOGICS CAPACITY IS NO FIELD OF DREAMS

On the surface, Andrew Skibo's decision to join AstraZeneca (December 2007) may seem somewhat odd, especially when you consider his expertise is in the manufacture of biologics. He had spent the previous four years restructuring and rebuilding the corporate engineering function on a global level for Amgen — one of the world's oldest and biggest biotechs. AstraZeneca, on the other hand, with a small molecule blockbuster bullpen which included the likes of Crestor, Nexium, and Seroquel, was most certainly still perceived as Big Pharma. But Skibo arrived in the role of VP of global engineering at MedImmune, a biotech AstraZeneca had acquired seven months earlier to bolster its biologics product portfolio and position the company for long term growth. (He didn't achieve his current title until a few years later.)

But executing AstraZeneca's biologics strategy required more than the acquisition of a pipeline. Because, unlike the *Field of Dreams* film where a baseball field is built on the prophecy, "If you build it, they will come," our industry requires more than a premonition, as the FDA's mantra is not, "If you build it, we will approve," and the stakes for miscalculation are significant. "To plan for the capacity you need," says Skibo, "you're looking at very large investments which can be on the scale of hundreds of millions of dollars." For example, Novartis eclipsed the $1 billion mark with the completion of its Holly Springs, NC vaccine manufacturing facility. MedImmune invested more than 2.3 million man-hours in the building of its large-scale mammalian cell culture-based production facility in Frederick, MD (ISPE FOYA, 2011). In the cost-conscious pharmaceutical industry, these kinds of investments of time and money are rare. And when so many dollars are spent on one project that means there are fewer for others. "You don't like to make these investments any larger than you have to," Skibo states. "But if this capacity is the only way you can provide enough material to launch a new product, you must make the investment."

For the folks at AstraZeneca, the challenge was developing detailed models that took the guesswork out of what kind, how much, and when that capacity was needed. According to Skibo, a good risk-based biologics manufacturing capacity planning model should take into account not only how big an investment is needed, but how late you can possibly postpone the investment to minimize risk given the distinct possibilities of a drug failing to be approved or underestimating market need. Ironically, Skibo admits that the model's planning process, which began in 2009, came at a time when the company had a great deal of excess capacity, so much so, that in 2012 the company announced the development of a trusted partner network. The 15-year agreement with Merck allowed the two companies to use each other's biologic facilities in production areas where there is a capacity shortfall. "We are selling the excess capacity we have and all the while modeling for when we will have to add more, because the timelines in our industry demand it."

SOMETIMES IT PAYS TO DISCARD CONVENTIONAL WISDOM

When Oakland A's major league baseball manager Billy Beane boldly discarded conventional wisdom and embraced advanced statistical analysis, he was soundly criticized by baseball purists until he demonstrated that it worked. Similarly, the pharmaceutical industry is filled with traditionalists and is often — very — slow — to — change. Take the simple biologics capacity planning model, for example. It would say that a plant the size of AstraZeneca's MedImmune facility in Frederick running a legacy biologic process and producing one product straight for a year has 65 lots of annual capacity. "You have to factor in a two-week shutdown for quality and maintenance and running at a rate of 85 percent of full capacity to allow for some slop," notes Skibo. But the reality is — this model is based purely on the knowledge gained through experience. Companies like Amgen and Genentech have plants very similar to the MedImmune facility in Frederick and have been in operation for the better part of two decades or more. "It's a fairly standard four pack plant," he states. "We all have 4x15 or 6x15 thousand liter bioreactor plants." Tell an industry veteran like Skibo at what rate of capacity

> "We are selling the excess capacity we have and all the while modeling for when we will have to add more."
>
> **ANDREW SKIBO**
> Regional VP Of Supply Biologics, Global Engineering, And Real Estate At AstraZeneca (AZ)

Great Communication Is A Learned Skill

THERE ARE CERTAIN VOICES THAT POSSESS SUCH A DISTINCTIVE QUALITY that upon hearing them you can immediately discern their owner. However, it is not just the tonal quality that makes the voice unique but a variety of characteristics, such as inflection, pace of delivery, and the use of simple words to communicate complex subjects. Great communicators of my youth, Paul Harvey, Walter Cronkite, and Ronald Reagan, owned such vocal tools and the intellect with which to use them, backed by character traits of honesty and humility that made the message easy to understand and implicitly believable. Some might mistakenly believe that they were simply "naturals." But this is a fallacy. All of the people mentioned above worked very hard at their craft to become great at communicating their message. So too does Andrew Skibo, regional VP of supply biologics, global engineering, and real estate at AstraZeneca (AZ). He advises others to do so as well.

"We use a lot of executive coaching around change management and even presentation skills," admits Skibo. "I'm really big on that, especially for our younger employees." According to Skibo, you can have folks who are brilliant at what they do. However, if they can't take that brilliant solution out of their heads and communicate it to 50 other people so as to bring the team along with them, they're ineffective. "We have staff that ranges from people with 35 years of experience to people new to the industry," he states. "We invest a fair amount in presentation and communication skills so we can get them all communicating the same language to one another."

a plant is running, how many bioreactors and their size, and the number of legacy biologics being produced, and he can tell you how many lots the facility is capable of producing. According to Skibo, this is why the simple model is unduly biased and flawed. "In a year when we have seven tech transfers taking place," he affirms, "we were operating more in the 30-lot-per-year production range." Had Skibo applied the simplistic model for capacity planning, he would have thought he had 35 more lots available than actually existed, a real problem. In 2015, Skibo anticipates that this kind of planning will get even more complex, such as conducting two commercial runs, four clinical runs, and as many as three process validation runs in the same plant. "In a year like that I'll be lucky to reach 30 lots," he admits. Consequently, the MedImmune team knew it needed to throw out conventional wisdom and develop a more accurate model.

One of Skibo's first tasks was to get the biologics R&D, commercial, and clinical ops divisions operating as a fully integrated enterprise that was assessing the range of risk. He says this was an "ah-ha" moment for a lot of them because operations wasn't looking for an exact answer. "I wanted their best guess of what the

ranges were so I could go away and play with those risk ranges," he says. "So we could determine the probability of making it to the end. Early stage, you have a 12 percent chance; in Phase 3 you have a 58 percent chance. What gets complicated is when you are within two or three years, and you have to start making a binary risk assessment because there isn't such a thing as 58 percent success."

In addition to getting these various risk ranges, Skibo was seeking to create a model that allowed input of other details. For example, a process development (PD) clinical run cycle is typically 11 days. A "flatlined" production run is five to five-and-a-half days. "The old model didn't allow you to put that difference in," he states. "When it comes to turnaround times, are they 17, 11, or 7 days?" he asks. "If you only turn it around once every 18 months, it doesn't matter." However, if you have to turn around five times a year, the difference between 17 days (5 x 17 = 85 days) and seven days (5 x 7 = 35 days) is 50 days, which equates to nearly two months of production you think you have but in reality, don't. These are the things Skibo says you need to understand when planning for capacity with a risk-based approach. You also need to know where your benchmarks are now, how long it will take you to change them, and if the investment is worth the risk. "For example, a long-established product with an eight day process cycle could be improved," he explains. "But you would have to change the license to do so." Skibo suggests asking yourself how much of the biologic you need in any given year before you start trying to change the process (see sidebar — Shire Helps Skibo In Assessing Single-Use Risk).

In addition to having a deep understanding of what you need and how your plant runs, he advocates using a multilayered planning approach, especially on the large molecule side. Skibo believes senior leadership needs to drive the process for what the model needs to measure. Your manufacturing, science, and technology (MS&T) group — scientists who focus upon full commercial-scale process improvement rather than initial product development — should then develop the model. "As we concluded cases, factoring in risk data, the two ends of the team [senior leadership and MS&T] fine-tuned the model together to really get it to do what we needed," he adds.

KEY LEARNINGS OF IMPLEMENTATION

Only after creating your model and analyzing some of the data will you really understand what your plant can and cannot do. For Skibo, there were four key lessons. First, many of the products in your pipeline aren't going to impact overall plant capacity. "The ranges related to most small products are going to fall within the error (i.e., .7 to 4 lots per year) of the model," he explains. Much like a baseball player knows that getting walked won't hurt his batting average, managers can place these small products in the "don't need to worry about impacting capacity" category.

Second, you learn which products do impact capacity. At the Frederick facility there are three products that drive the need for capacity. "These I really had to worry about. I needed to get the numbers right going forward because the outcomes related to how many of them are successful will drive the need for potential and substantial capacity beyond what we have," he reveals. Third, and something Skibo says many bio-firms have now learned, "You need both the battleship [i.e., equipped with large bioreactors], and a plant with 2,500-liter bioreactors for the small products." This led to the fourth lesson. Small products consumed a disproportionate amount of "battleship-wasted capacity" due to turnaround time. "It was worth getting them out of the battleship and into the 4x2, 500-liter bioreactor plant that we decided to build," he affirms. There was yet another lesson that even an old industry veteran like Skibo admits he never even thought of.

ARE YOU COMMUNICATING IN THE SAME LANGUAGE?

If you have ever watched a baseball game, you will see the catcher flash signs to the pitcher, using his fingers. Sometimes, managers give signals to players on the field from the dugout. You might notice a first or third base coach using a combination of signs, such as touching his hat or pulling his ear to tell the runner or batter what to do. What makes it interesting is that each team can be using different signs to communicate the same message. But unless you know the sign, you won't understand. The same thing happens within our industry. And though we may be using words and communicating in English, this doesn't mean we are speaking the same language or being understood — something Skibo discovered when he met with the CEO and commercial team to discuss their findings. "Everyone has their own yardstick," he explains. "If I'm speaking to clin-ops, we speak in terms of doses. If I speak to PD (process development), it's in grams of protein. With clinical and research, we think of numbers of patients. Each one has their own metrics related to what this product means in their space." Skibo says he thinks in doses, then dosage-per-dose, then how much titer needs to run, and then he works his way through the math to arrive at the number of lots to be produced. To him this process seemed fairly straightforward. But when he was

Shire Helps Skibo In Assessing Single-Use Risk

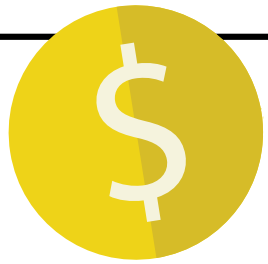
"FOR EVERY DECISION WE MAKE, we go back to the risk of certainty that we can deliver," shares Andrew Skibo, regional VP of supply biologics, global engineering, and real estate at AstraZeneca (AZ). "One of the most enlightening visits I've ever had was a lengthy tour of the Lexington Shire facility," he states. "They gave us a complete debrief of what it took to design and bring it online and what they learned in a year and a half of operation." What was illuminating to Skibo from this experience was the sourcing of single-use suppliers, something he thought seemed too risky when you have three new product launches depending upon available capacity. This is why when the company built its ISPE 2011 facility of the year plant in Frederick, MD it was decided to make it smaller and more flexible and to do so with stainless steel as opposed to single-use.

What Would You Do Differently?

TOWARD THE END OF MY CONVERSATION WITH ANDREW SKIBO, regional VP of supply biologics, global engineering, and real estate at AstraZeneca (AZ), I asked if he would do anything differently. His reply was immediate. "Yes. There are always learning curves. I wish we had seen the need to have a more detailed model earlier because we wasted six months trying to figure out why we were stuck at 28 lots a year of manufacturing capacity." Skibo believes the implementation of the new model for manufacturing capacity was such a game changer for the facility that he wishes he had responded to his instincts sooner. "It probably took us nine months to realize that most of our frustration was coming from the 'This is the way we always used to do it,' mindset."

When Skibo first focused on the actual capacity of the new Frederick, MD plant, the company was running at 28 lots a year — and it was accepted that this was the best it was going to do. "I came from Amgen," he states. "I know what a flatline plant can run. Talk to Genentech, GSK, and Biogen Idec, and they will tell you that a standard four-pack ought to be in the 60 to 70 lots a year range. At some point I realized, we're going to be having this debate a year from now, two years from now, three years from now. If folks don't understand why you can't get out of where you are to get to where you need to go, you'll never get there." The typical response in such a situation is brute force, which is dangerous in a biologics manufacturing plant because it's a quality risk. "If I had to do it over again," Skibo affirms, "I would have infused more new team members sooner."

explaining the model's results, the CEO asked, "Is this product constrained in capacity? It's one of the earliest launches we might have." Skibo's answer, "Don't worry about it, because it's .7 to 4 lots." The next question revealed that Skibo wasn't speaking in the same language. "What are 0.7 lots in revenue?" the CEO asked. Skibo didn't have that math in his head, and he realized that the model needed to be further fine-tuned so it could generate results in the internal languages that were meaningful to everyone. "We added to the model what the lots per billion dollars in revenue are because, at that very top level, they think in terms of how much we will sell," he states. "That's the math they deal with on a daily basis." Regarding the commercial side of the business, Skibo learned they too have their own language. "If I'm speaking to commercial, it's not just patients, but number of patients served," he shares. His advice: When developing a model using a risk-based approach to plan for capacity, make sure you know whom you are speaking to and that the model generates results in the appropriate language. Doing so will result in a better plan for manufacturing capacity, and ultimately, patient access to your company's biologics.



The Art of Optimizing Small Biotech Market Caps

— From Scientific Dreams to Strategic Reality

Last month, in Part One of this discussion, our panel of company executives and investment experts examined the key factors that can determine a small life sciences company's valuation and market cap. As the sun rose outside the large meeting room window overlooking the San Francisco skyline, our roundtable — held during the confluence of industry events surrounding the JP Morgan Healthcare Conference in January 2014 — continued to explore the effects of valuation and market cap on such a company and what it can do to optimize its value at every stage of its development.

The remainder of this thought-leader discussion covered the effects of valuation and market cap on companies as they grow and on ways they can optimize their value at every stage in their development. More case studies and experience-based lessons arose in the next half of the discussion, along with worries about drug-candidate shortages and unsustainable investment cycles. Here, the panel detailed the importance of managing company and scientific communications, establishing relationships, spending cash carefully, and other actions companies can and should take to optimize their value and growth.

Moderated and edited by
WAYNE KOBERSTEIN Executive Editor


A Life Science Leader
Editorial Roundtable
PART 2

Our panel consisted of the following people — the ones who answered the invitations we had sent out to a range of people reflecting the leadership of small and large biopharma companies and investment firms:

A Dennis Purcell Senior Partner of Aisling Capital
B Rich Vincent CFO of Sorrento Therapeutics
C Jacob Guzman Corporate Client Group Director at Morgan Stanley
D Allan Shaw Managing Director at Life Science Advisory Practice, Alvarez & Marsal LLC
E Ford Worthy Partner and CFO of Pappas Ventures
F Kenneth Moch President and CEO of Chimerix
G Jaisim Shah CEO of Semnur Pharmaceuticals
H William Marth CEO of AMRI
I George Golumbeski Senior Vice President, Business Development at Celgene
J Henry Ji CEO of Sorrento Therapeutics

STAGES OF VALUE

Another case of start-up financing illustrates how a track record of credibility helps founders through the critical points of company valuation. But panelists still worry about the inevitable effects of the life science business cycle. The moderator turns to entrepreneur Henry Ji, CEO of the new start-up, Sorrento, for his view of early stage investment and valuation.

WAYNE KOBERSTEIN: Henry, how are companies affected by the valuation that they receive at any given point?

HENRY JI: I'm going to answer by describing some innovative ways we used to raise money at different stages. We were raising our money in 2009, during the financial crash, but we had no VC, because the VCs at that time were more realistic — they wanted only late-stage programs. There were no early-stage dreams; you cannot sell dreams, with only a patent in hand. So we went to individuals and groups, basically. We went to the experts in the therapeutic antibody field because we were building our own therapeutic antibody library. We went to the father of the human antibody library, the inventor for the catalytic antibody library technology, who is Richard Lerner. He liked our dream, and he picked up a phone to call Phil Frost. That's how we got our main investor, who never worried about the financial crash.

Phil put us into a shell company, with the valuation fluctuating from $10 million to $400 million, when we had about 300 million shares outstanding, so we would not know what our value was. That was easy to sell to our initial investors, but not to the VCs, which is why we didn't have any VC investors at first. So it was a tough one — selling a dream — especially because we didn't even have a clear strategy yet, only the dream of building the antibody library.

A couple of billionaires were the first ones who funded us. We started our dream with a $10 million valuation. At that point you have to figure out how to really get going; that's when the strategy kicks in. You cannot sell dreams forever. You have to be realistic. Last year, we did three transactions to help us transform the company from a discovery company to a late-stage oncology development company. We were looking for some early leads into new therapeutic antibodies, but that takes a very long time, so we bought a late-stage oncology product that is a next-generation formulation of paclitaxel, Cynviloq, and a Phase 1/2 cancer-pain management product, resiniferatoxin, and strengthened our antibody platform with ADC or antibody drug conjugates platform, making us the leader in the ADC space.

VCs are tough to talk to because they are very realistic. You know, they want to see the data, preferably late-stage data. In between the early investment and seeking venture capital, we had an alternative strategy. We went to China. Most of the time, Chinese investment is relationship-based. Once you establish a relationship with the Chinese investors, the valuation is much easier to build. The beauty of this strategy is it gives us alternative resources to what we have here in the United States, where the valuation is very low. So now we've got a decent valuation, we have our money, we can move our program forward, and we can continue to do some transactions. That helps a lot. Without the valuation, we could not do some of the deals we have done on the acquisition side.

KOBERSTEIN: So, at what point does valuation and market cap become important in a company's development, and in what ways does valuation affect how a company develops?

PURCELL: There comes a time in every company's evolution — when the stock is high, you sell the stock, and that relates to the cost of capital. It's a very interesting question, again, with Intercept; they can sell two million shares and raise a billion dollars and be like one of the biggest companies in the world, at least for a day. So when the valuation goes up like that, you've got to figure out a way to take advantage of it.

SHAH: And you maximize that by saying that the sky's the limit, or do you try to

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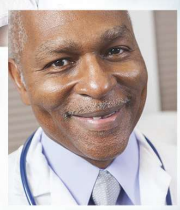

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PURCELL: One of the things I'm worried about is that we're in a great period right now; this is a big time for biotech, but we've also been through years and years where companies have only six months of cash left. When there's less money, the optionality goes away. I would give three main pieces of advice to companies: One, right now, when you're well-capitalized, pretend like you only have a month of cash left so you don't waste the cash. Two, I believe we have to reassess governance at these companies. We talked a little bit before about the business versus the science — get the right board members. And three, now is a good time for companies to develop more options for where you might take the business going forward.

SHAH: But isn't it great that we can see this turnaround?

PURCELL: It's relatively consistent.

SHAH: It is amazing how quickly the general climate can turn around, right?

PURCELL: Well, here we are at the beginning of the year and everybody's euphoric — there are 33 companies trying to press for an IPO in the next 30 days. But this thing could turn on a dime.

KOBERSTEIN: As does the chatter that goes on in the press . . .

PURCELL: We may have 100 companies trying to get out in the next two months, so that's got to create a bit of an issue. The class that went public in '13, they're all good companies. The question now is, are we moving down to the second tier of companies? And what does that mean? Their investors are just going to get tired.

MOCH: We're hoping to differentiate. In a way, your second-tier theory is logical, but it remains to be seen.

PURCELL: Already, as we saw toward the end of the year, the generalist investors have started to get out of the sector. In December, we saw stocks trade down, and a lot of that has to do with the generalist investors leaving. We are all looking to see what happens to the next 30, 40, 50 companies that are trying to do an IPO.

MOCH: The essence of it all is that nobody has ever invented a cure for the business cycle.

PURCELL: But that's what we have to do; we have to figure out, as an industry, how to stop this vicious cycle. It would be so valuable for everyone. But we've been saying that for 25 years.

MOCH: The quandary will not go away because it's a requirement of the SEC that we release such information. Remember, this is one of the few industries where, because of the long timelines to develop a product and the requirements for capital that go with that, everything is public and everything matters, which is why we're always watching dramatic fluctuations in company stocks. A public company has a material obligation to disclose that it just did a small Phase 1 trial that had six patients who performed well. If you don't let that information out, you get to go to jail for withholding material information that could affect your stock price, and so it does. At a Big Pharma, you would say just let it stay deep in the bowels of the company, but for a biotech company with a small number of people, it is the key material event dictating the future.

KOBERSTEIN: Okay, let's say I'm a small life sciences company, Koberstein Biotek, and all of the megatrends and movements we've discussed affect me — the business cycles, booms and busts, and other external factors. But what about the factors that are peculiar to my company? I want to know what I can do to influence the valuation of my company and make it what I believe it should be at any given stage. Is it about getting enough press? Is it about getting my story out? Is it about networking with others in the same sector?

MOCH: I'd like to see what the investors say about this, but I think the biggest influence on probability of success is what Dennis was saying — it's having capital — and everything else flows from that. I do believe in the capital-asset pricing model. If you look at all the risks for a company, the biggest risk is lack of capital. As Brook Byers [senior partner, Kleiner Perkins Caufield & Byers] said many years ago, "The greatest challenge for a CEO is not that a trial doesn't work, it's not having the capital to prove that it might have worked." I've always liked that statement, because that's our job. Gathering enough capital to conduct the best possible clinical development. There is the vision; there's talking to people, there's making noise and being heard, having 50 meetings in four days, and all that — but if you don't have the capital that gives people the confidence you can get through to the end of the experiment — the clinical trial — then nobody really cares. Having the capital to get to something is different from having something. That's the interesting dynamic of this business.

SHAW: To underscore Ken's point, too often companies try to time the market when they access capital, and I don't believe this should be done. When the ducks are quacking, you have to feed them. You have to seize the opportunity. People get stuck looking in their rear view mirrors at yesterday's valuation; they don't look ahead at the opportunity, and it passes them by. One company had a nice run-up in valuation and became fixated on reading their press clippings, believing their product would go forward with an accelerated approval and thinking maybe it would raise its money then. And my advice to them was, don't time it. Just take it when you can take it. And unfortunately things did not evolve for them as hoped, and their valuation slid back down again. So yesterday's value now looks a lot better than today's.

PURCELL: We see that a lot. Companies come in and say, our pre-money is $100 million, period. So, we say, "All right." And nine times out of ten, they present again with much more reasonable expectations. I've got a little hint for your new company, Wayne. There are 8 million accredited investors in the United States and only 2 percent of them own a private placement. So my prediction is, because of the JOBS Act and because so many companies are starting up, crowdfunding will be important to your new company. You might raise your first $5 or $10 million not from VCs, but through the crowd, because it's a huge untapped market, and there are companies now being formed to take advantage of that market. So that's how you raise your money and get started.

GUZMAN: That's an interesting point, because my clients are saying exactly the same thing, over and over and over again.

PURCELL: I see it coming.

GUZMAN: I've had so many attorneys and executives come to us looking at the untapped accredited investor market.

Everyone from venture-backed companies to the large players like the Carlyles of the world. These groups are saying they know the institutional players well, and the accredited market is the one they're focusing on next.

OPTIMIZING VALUATION — PATIENTS ON YOUR SIDE

KOBERSTEIN: Patient advocates, long the natural allies of companies with new treatments in areas of high medical need, are now taking a more direct role in value-setting investment.

WORTHY: The conventional wisdom is that you can probably start companies through crowdfunding, but when a company gets to the point that it needs to raise $30 million, as Jaisim did, that may be, and probably is, unrealistic. Wayne, you mentioned the press and the degree to which the press can play a role in affecting valuations. The press written about a particular company has everything to do with creating expectations. From many investors' perspectives, what is said in the press that has information value is one thing, but in creating expectations that really affect the way that we're valuing companies, probably there's a minimal impact. However, it is important and in some cases critical for a company to manage expectations in the press very carefully. Companies that do it well can actually create value, but not in the way that you might imagine.

We are fascinated these days with the degree to which patient advocacy groups are beginning to play a real role in the development of drugs. The role involves bringing money or influencing money to come to the table, and it also involves raw political pressure. We saw it with Plexxikon, a company that we invested in a number of years ago. Plexxikon let a reporter from the *New York Times* be almost embedded in a long clinical trial it was conducting, and the *Times* came out with a fascinating three-day series on the trial. We believe the effect that this coverage had, not directly on investors, but on patients who were clamoring for this melanoma drug, and the way that this pressure and interest rippled into the FDA, through Congress, and so forth, positively and dramatically affected the speed with which the company got the drug approved.

We also believe the *New York Times* story lent a unique validation, in this case, particularly from the perspective of Japanese investors, and ultimately a Japanese company acquired Plexxikon. So it's obviously important to manage expec-

tations through what is disseminated in the press. It can be a two-edged sword, but that's an example of how patient advocacy groups, through learning about a company through the press, can have an impact on the speed with which a drug is approved.

WRIGHT: The lesson is, if you want to improve your drug's probability of accelerated approval, embed a reporter as a mediator variable to your clinical trial! (Laughter.)

MOCH: I'm on the board of BIO [Secretary, Emerging Companies Section Governing Board], and there's a lot of discussion there about patient advocacy groups and bringing them more deeply into the process. I have no doubt you are seeing it day in and day out at Celgene, George, with the patient populations you serve. They want to be involved, they do help in fundraising and informing patients, and they have a voice with the regulators. There is no doubt they have a voice at FDA advisory committee meetings. They also have a voice in our particular drug-disease area where, because the conditions are life-threatening, the drugs are allowed to be used compassionately. You'll be shocked by the number — we have 430 compassionate uses — which a larger company wouldn't do. It's just the way we evolved. But we stopped that program because the FDA asked us to go out and collect all the clinical data from the compassionate-use patients, and it was costing too much, unfortunately. We still get 10 calls a week from doctors who want this drug. And clearly they're also calling the FDA, which wants us to figure out a way to either deal with it or stop people from calling in all the time. But that type of clarity of unmet need is very important in the approval process. You can't underestimate the voice that patients have.

KOBERSTEIN: I recently interviewed Janet Woodcock, and I asked her about the FDA's implementation of accelerated review in specific cases, including Sarepta. She said something very similar to what I've heard here, which is it's all about the data. She said there are so many companies wanting accelerated review now, and the agency is examining each company's data, comparing it to the others. If the company's data isn't up to the same standard as another, it's likely to be denied, no matter how intense the patient advocacy.

MOCH: That's their job.

KOBERSTEIN: Yes.

MOCH: But patient advocacy still puts it on the FDA's plate to make a decision or to review it. And patients do have a voice — whether the voice is good, bad, or indifferent. I'm sure you have a whole patient advocacy department in your company, George.

GOLUMBESKI: We do have a very strong advocacy group, and they will continue to be important down the line. In fact, they are very helpful in helping us remember what we are working for. But in the end, in my opinion, that will not get a drug approved. My own personal view is too many small companies spend too much time and lost motion deliberately trying to pump up their stock price. If I had a penny for every press release I've reviewed in my career based on 10 patients with almost a claim that DDMAC (Division of Drug Marketing, Advertising and Communications) would get on, suggesting there's efficacy ... I completely agree with everything Ken said, but just look at all the press releases saying, "We got an SPA [special protocol assessment]." That's probably a material event, but it is relatively easy to get an SPA in a very high unmet medical need condition. And does that mean you have a drug? No, it means you're going to do a trial. With cancer trials, 50 percent fail in Phase 3. I'm not saying they shouldn't do a press release. But generally, trying to suggest that the drug is working after testing it in 3 or 30 patients is a mistake.

PURCELL: The multiple myeloma people have their own venture fund. So not only are patient advocacy groups going to be involved, now they will be starting their own funds.

MOCH: And they're going to move from funding basic research to funding clinical development in big ways, across various areas.

GOLUMBESKI: A year ago, we started working closely with LLS, the Leukemia & Lymphoma Society, and we also have a lot of interaction with MMRF (Multiple Myeloma Research Fund).

KOBERSTEIN: If it's a group like the Prostate Cancer Foundation, they will have the right expertise in-house, but there are other groups that may not be qualified, so what you're describing may be somewhat of a chaotic situation.

PURCELL: One of the questions on the investing side is, why should we reinvent the wheel on multiple myeloma? They know everybody. Why should we examine these companies one by one? Why wouldn't the venture community partner up with the disease foundations, because they are the experts. They know everybody. They know what's hot, they know what's not. I think you're going to see more of that kind of collaboration between the investors and patient advocates.

GOLUMBESKI: Some of these groups are run by really excellent medical directors, really smart people.

SHAH: It's also not inconsequential. We were talking about the business cycle, when the capital markets and the venture funding is available and then not available. The patient advocacy groups will go a long way to bridging that gap as providers of a longer-term funding mechanism for innovation over time.

KOBERSTEIN: So, in other words, anybody who brings capital to the table is welcome, right? And you deal with the details later?

SHAW: I don't think anybody who's in need of money is going to pass it by, as long as it's from a legitimate source.

KOBERSTEIN: The last question is, "What actions can companies take to achieve or optimize their market cap at the key stages of development?" You gave me some good points for Koberstein Biotek. Are there any other things my company can do that we haven't covered?

MOCH: George was talking about it in an interesting way: Although we are required to communicate, it's the quality of the communication that counts. But it's not formulaic — how you write the releases is subject to interpretation, accounting for some of the things that make us all squeamish. Sometimes I get nuts when I see a company make claims early on in a press release, and its stock goes up, or they raise money. Is that really fair, versus a more conservative approach where you don't get that bang? It is an enigma, because the market often reacts positively to creatively written press releases, and yet,

they raise capital. And to come back to the earlier point, capital is the most important element in creating value and being able to get through development.

WRIGHT: To Ford's point, the reason the trial he referred to had so much value wasn't just because the *New York Times* reporter was there, but because it was somebody outside of the company serving as a witness. The lesson might be, who can you get outside of your company to start talking about your product?

MOCH: In his example, Ford was talking about an extraordinarily serious situation, which would boost the valuation.

GOLUMBESKI: We have to remember how brutally devastating metastatic melanoma is, and this was the first drug that worked in some patients. That is a pretty hard situation to ignore. But my point about stating early results — we may be seeing the issue illustrated now in the Novartis-UPenn collaboration with CART in B-Cell disease. Out of the first 10 patients or so, three or four of them were end-stage, and they're in complete remission now. That has been in the *New York Times* multiple times, as it should be, because the results are truly groundbreaking, even if the number of patients is small.

A CEO I know once said, "I've raised money when I could, and I've raised money when I had to, and believe me, it's a lot easier to raise it when I could." We take the same attitude with respect to building our pipeline. The reason we're so active now is none of us knows how long we're going to be in this financial position, but we're in a position where we can build our pipeline, and we have to do it now, because God help us if we're trying to do it when we have to.

WORTHY: I was just going to say, my point was not to embed a *New York Times* reporter in every trial, but it was really the larger point of how good management of communications, not only with the press, but also through social media, can stimulate activity among patient advocacy groups.

MOCH: As an industry, we are going to figure out the right focus. The leadership at BIO is working right now on producing an industrywide view of the best practices for company engagement with advocates during drug development.

KOBERSTEIN: And likewise, this discussion we've had today is just a part of an ongoing industry conversation on best practices in creating value and seeing that value reflected in your company's valuation and market cap. I thank you all for coming and for participating in this enlightening exchange. We will be presenting this discussion on-line and in the pages of *Life Science Leader*, and we will continue to take up the same topic in other venues in the future. Good day.

An Introduction To Pharmaceutical Parallel Trade In Europe

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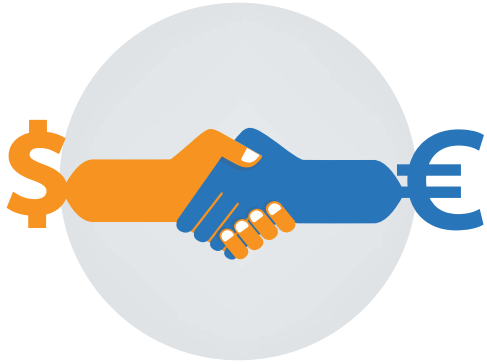

Parallel trade, the free movement of goods across Europe from lower-value to higher-value markets, has had a major impact on the European pharmaceutical industry since the 1970s.

Parallel trade is viewed rather differently by pharmaceutical companies and parallel traders, and this made for some contrasting perspectives at the SMi Group's 8th Parallel Trade conference, held in London in February 2014.

WHAT MAKES PARALLEL TRADE POSSIBLE?

The legal framework behind parallel trade dates back to the 1957 Treaty of Rome. While patents can protect against parallel trade in other markets, it cannot be forbidden within the EU. This is because of the free movement of goods, one of the basic tenets of the EU, explained Eric Noehrenberg, director of public affairs for market access at Shire and conference chair.

"The EU has established a policy of 'community exhaustion' of most forms of IP. This means that once a firm has put the drug on the market in any EU country, it may not prevent the sale of that drug within the EU by any other firm by claiming a violation of patent rights or trademarks, under most circumstances," says Noehrenberg.

What makes parallel trade a feasible business model is the price differential across the EU. This can be driven by local pricing legislation, such as the capping of drug prices in Greece or through price negotiation with manufacturers as has happened in Germany. Fluctuations in currency values for EU member states not using the Euro also can make them targets for sourcing or selling parallel-traded drugs.

Traditionally the source countries (those with the lowest prices) have been Greece and Spain, but the destination countries do fluctuate. For example, according to Noehrenberg, there was an increase in the share of parallel imports in pharmacy sales in Denmark, Ireland, Netherlands, and Sweden between 2009 and 2011 and a decrease in Latvia and the United Kingdom. Finland, Norway, and Germany remained stable.

"Overall figures can be misleading, as there is strong variation among products and markets. For example, some products are more than 90% parallel imported into Denmark," Noehrenberg adds.

THE BIRTH OF PARALLEL TRADE

As discussed by a number of the presenters, the first parallel-traded drug was imported from the U.K. and sold in the Netherlands in 1975 by Adriaan de Peijper, a Dutch importer. While the drug was authorized in both the U.K. and the Netherlands, de Peijper did not have the product-marketing approval documents or the batch records, which resulted in a legal battle. He argued that he had not been able to access the documentation, and the case was referred to the European Court of Justice (ECJ). The ECJ said that demanding the documentation was unnecessarily restrictive and thus ruled in favor of de Peijper. Following the case, the European Commission produced a text outlining the basic principles for an abbreviated form of marketing authorization for parallel trade, including that the drug must have the same active ingredient, route of administration, and therapeutic effect. The information included with the drug package should also ensure that it's traceable.

As an example of an early adopter of the parallel-trade business model, the story of EurimPharm started with a cough. German pharmacist Andreas Mohringer, on vacation in the U.K., bought a bottle of cough medicine and saw that it cost a third of the identical product at home. This gave him the idea of creating a company to import pharmaceuticals from lower-cost countries to Germany, a higher-cost destination.

In 1975, he founded EurimPharm with a loan of about $3,000 from his parents. He started by importing Valium and repackaging it in his living room, but his homemade packaging infringed copyright laws, and he was taken to court. After this, he made sure that the packaging complied with trademark laws. In the late 1970s, Mohringer was able to give up his day job, and by 2011, he had around 500 employees repackaging 6 million prescription drug packs a year.

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PARALLEL TRADE: DIFFERENT PERSPECTIVES

The debate at the conference became quite lively over the upside and downside of parallel trade when viewed from both the trader's and the pharmaceutical company's perspective. The global squeeze on national healthcare budgets as a result of the financial downturn and the aging population has provided an opportunity for parallel importers. Namely, they argue that their presence in the market results in patients having access to lower-cost drugs. This is of particular benefit in countries with lower GDPs or in countries where patients pay or co-pay for their own drugs. The traders also say that they address access inequalities across Europe by exporting drugs that would not otherwise be available in given markets.

From the pharmaceutical company's perspective, parallel trade reduces their income from the higher-value markets, which cuts their return on investment and therefore, the amount they can plow back into the development of new drugs. This in turn, potentially reduces the number of alternative drugs that are available to patients and payors in the future.

In the lower-price source markets, according to the opponents of parallel trade, traders who buy up stock from pharmacies, hospitals, and wholesalers may reduce stock levels to a point where local patients have trouble accessing drugs (see *The Rising Problem Of Parallel Trade* in *Life Science Leader* March 2009). This imbalance of supply and demand can lead to price increases, which have an impact on both patients and payors. However, the increased demand in these regions does, at least, help to offset the pharma company's losses in the higher price countries.

"Initial price-setting and reimbursement levels are established in light of market conditions in specific national markets so that patients in those markets can have sufficient access to the medicines they need. Parallel trade upsets this delicate equilibrium designed to meet patients' needs for timely access to medicines," says Noehrenberg.

The patient also brings a perspective to parallel trade. In a discussion about ethics, a number of presenters and delegates reported patient concerns, including drugs that arrived in boxes with foreign language text; tablets that were different colors, shapes, or doses; or blister packs with labels over the foil that made the packaging harder to handle for older patients with less-nimble fingers.

ROUTES TO MANAGING PARALLEL TRADE

As Janice Haigh, practice leader, market access for Europe at Quintiles, explained, there are three different approaches to managing parallel trade — through price, friction, or volume. An example of the price approach has been used in Spain, where manufacturers have given wholesalers a discount if they can show that all of their sales are within the country's borders.

Managing by price can be uncertain for a number of reasons. Reducing or removing price differences across countries in Europe will reduce parallel trade, but it can affect the ability to get reimbursement and may adversely affect poorer markets by pricing drugs out of the market. Some companies have tried using dual-pricing strategies, for example, through rebates, but this can get complex.

The friction approach, which aims to make drugs from cheaper markets less attractive to higher-cost markets, includes changing pack sizes or doses, or supplying simpler or lower-cost forms to markets where drug prices are lower. This is unlikely to deter traders, increases the cost of manufacturing and supply, and reduces the attractiveness of the drug in the local market. The friction approach can also include legislation. For example, in April 2013, the Romanian healthcare minister blocked the parallel export of oncology medications, in response to trade in 2012 that exceeded €.5 billion.

Another friction approach is through collaboration. An example of this is a direct-to-pharmacy sole distributor agreement, such as that signed by Pfizer and UniChem in the U.K. in 2007, despite a last-ditch attempt to block the agreement from a number of wholesalers.

"[Parallel Trade is] about getting the right products to the right place, locally."

TIM HAMMOND
Head of Global Pricing and Tendering at LEO Pharma

The simplest approach to managing parallel trade is by controlling the amounts of a drug that are in the market so that the excess is not available for traders. This has the added advantage of creating manufacturing efficiencies. However, not everyone agreed with this approach. According to Donald MacArthur, global pharmaceutical business analyst for JustPharmaReports, control of parallel trade means that drugs are taking a lot longer to arrive to pharmacists in the U.K. because the process is longer and more complicated. He added that limiting supplies and suppliers leads to shortages, not parallel trade.

THE FUTURE OF PARALLEL TRADE

What does this mean in the United States? This form of parallel trade is unique to Europe and its free movement of goods, and so the major impact for U.S.-based companies is likely to be a reluctance to launch drugs in lower-cost markets in Europe. However, there have been attempts to allow similar approaches to parallel trade between the U.S. and Canada.

The challenge for the future of parallel trade will be to create a balance that benefits both patients and companies, with decisions based on research rather than anecdote. "It's about getting the right products to the right place, locally," says Tim Hammond, head of global pricing and tendering at LEO Pharma, as part of a lively debate at the conference. "We are here for the benefits of patients, and so we need better data and more dialogue."

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Angel Investors Look At Biotech

GAIL DUTTON Contributing Editor
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Angel groups are investing in biotech and are staying involved longer than ever before, creating new collaborations and financing options that raise more money than initial and subsequent rounds. Some say that today's angels are similar to venture capitalists in the early 1990s.

"Angels have become an increasingly important part of the financing ecosystem," notes Barbara Fox, Ph.D., founder and CEO of Avaxia Biologics. "More early-stage money now comes from angels than from venture funds."

That situation was caused by the convergence of trends that have made massive changes in the early-stage investment landscape, says Christopher Mirabile, managing director of Boston-based Launchpad Venture Group. Those changes include:

- difficulty floating traditional IPOs of less than $100 million
- ballooning size of venture funds
- fostering of entrepreneurship (through university classes)
- lower start-up costs for tech companies
- individual angel collaboration in networks
- network collaboration through syndication.

"When these trends combine, you have savvier entrepreneurs, companies that require less money, and angels with more money to invest," Mirabile says.

Fox recalls that angel groups were initially wary of investing in life sciences because of the long, risky development timelines. That began to change in late 2010 when Merck bought Smart Cells for $500 million. At the time, Smart Cells had a glucose-sensitive form of insulin in preclinical development. "That acquisition changed how investors looked at therapeutics," Fox says, and Avaxia has benefited. "We've raised $18 million from angels. Venture funds joined in the most recent round."

Savara Pharmaceuticals also is angel-funded. So far, it has raised most of its money from four angel groups, including $17 million to support its Phase 2 clinical program for AeroVanc, an inhaled vancomycin for MRSA infections in cystic fibrosis patients.

ANGELS' KNOWLEDGE DEEPENS

Often maligned as unsophisticated biotech investors, today's angel investors have honed their skills and pooled their strengths, building savvy groups that are both willing and capable to fund follow-on rounds. They have, in fact, much in common with the venture capitalists of 15 to 20 years ago.

Rob Neville, CEO of Savara Pharmaceuticals, has pitched to angel groups in Istanbul, Monaco, and the U.S. "In the early days, angel groups were disorganized. A few folks would get together, talk, and perhaps invest. Now they have a well-defined process for conducting due diligence and making investment decisions."

San Diego Tech Coast Angels, one of the largest angel groups in the U.S., has members with tremendous areas of specialization, says Jack Florio, board of directors. That includes insights into biotech as well as analytics.

Florio says members sometimes work privately with companies not yet ready for angel financing, providing management expertise and industry contacts. "We do a lot of mentoring, even with companies we don't invest in." The Seed Track grew from such efforts. This fund is dedicated to providing management expertise as well as financing of up to about $200,000.

SYNDICATION INCREASES FUNDING

The Angel Resource Institute's Q2, 2013 Halo Report, indicates that angel groups syndicate 74% of their deals. "Angels have realized there's real power in working together in groups," Mirabile says. "It can be hard to get sufficient deal flow yourself, but syndication lets groups pool due diligence and makes it easier to negotiate terms sheets and support companies."

For example, although the five chapters of Tech Coast Angels function independently, once a company is screened and approved as a potential investment, the terms sheet is presented to each chapter, thus increasing the potential size of the fund.

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"Avaxia has a national syndicate of angels that is filling a real gap as venture funds have moved away from early stage," Fox says. However, she cautions, although many funds have provided second-round financing, there's no guarantee they will be willing or able to fund subsequent rounds.

Many of Savara's original investors have participated in multiple financing rounds, even as the rounds have grown and additional investors have come in. The first round of $1 million was raised from about 12 angels in 2008, Neville says. All but one continued into the second round, which was $2 million. Funds raised continued to increase, and additional angels joined the program.

The most recent financing round (March 2013) was oversubscribed, so the company increased the round from $13 million to $16 million. The second tranche of this series B financing attracted Tech Coast Angels and the North Texas Angel Network, in addition to continuing investors from the Central Texas Angel Network and The Keiretsu Forum.

"Our next round may include venture financing or a crossover investment prior to a potential IPO," Neville says. Considering Savara's stage of development and its future funding requirements, a well-established institutional investor is necessary, he says.

Savara's funding rounds have been significantly higher than average for angel groups. The most recent Halo Report, for the third quarter 2013, released in January, reports median rounds of $520,000, down from $570,000 the previous quarter. The range of actual funding is wide, however. Florio reports Tech Coast Angels have funded rounds ranging from $250,000 to $1.5 million.

NEW DE-RISKING STRATEGIES EMERGE

"As an angel investor, you look for perhaps one in 10 investments to become big hits and a couple to have reasonably good returns. Half of the rest will die, and the remainder will muddle along without an exit," Florio says. New strategies are being developed to reduce that risk.

Shared risk pools are among the newest trends. William Podd, executive director of Landmark Angels, Inc., says, "Investment groups often will find five or six companies working in a similar disease area and pool them into one investment fund." In this situation, they typically bring in a big pharma investor to provide part of the due diligence and a possible exit strategy. "The investors bet that one of the companies will succeed and accept that as an exit strategy for the entire group."

This form of shared risk is so new there's been no research regarding what happens to the companies in the pool that aren't part of the pharma exit. Podd is asking that question now. Logical options, he says, are to go the next round as normal or take their portion of any payout and pursue further development on their own.

Financings based on sharing revenues or royalties are two trends Mirabile is seeing. Rather than selling stock in a company, the firm essentially borrows money and pledges to pay a specified portion of revenue to investors until an agreed-upon return is reached. The downside, he says, is that "this approach may siphon off cash that could be used for growth." Another financing option sells investors the right to buy stock for a predetermined price at some future date.

CROWDFUNDING

Mirabile considers crowdfunding complementary to angel investments and another way to bridge the financial gap between seed funding and venture capital. Until last September, crowdfunding had a way to raise money for specific projects and was popular among independent artists trying to fund music videos and indie movies. With the JOBS Act and enactment of its Title II provisions, crowdfunding became a viable fundraising option for companies wanting to tap accredited investors.

When Title III guidelines of the JOBS Act are approved, nonaccredited investors also will be permitted to invest. Their investments will be limited, however, and based upon income. Those earning less than $100,000 annually may invest up to 5% of their income or net worth, while those earning more than $100,000 may invest 10%.

Poliwogg and similar private exchanges are emerging to provide liquidity, not investment advice. The exchanges will make financial documents available to aid due diligence, but investors have direct relationships with the companies in which they invest, just like angel investors.

Angel groups are watching these developments and, cautiously, are beginning to use crowdfunding for some deals. "An angel group may list a deal to find angels outside its region to increase the potential funding amounts," Mirabile says. This strategy is effective only when the round already is well-established and has attracted good-name investors.

INVESTMENT PERIODS LENGTHEN

Angels historically invested in a company for two to three years. Now that time frame has expanded to five or six years, according to Florio. The reasons are many. "Venture funds have more money to work with, so they need bigger opportunities," Mirabile points out. Therefore, angels stay involved until companies can reach the point of attracting a venture fund or Big Pharma investor or floating an IPO.

Despite angels' willingness for longer-term involvement, they still prefer quick turnarounds with minimum risk. "Angels have stopped focusing on the home runs," Florio says. Instead, many of them are willing to accept moderate payouts with less risk. They often prefer to negotiate with a strategic buyer rather than take the product to the next milestone.

That's why the Big Pharma involvement is so important. It provides the possibility of an exit strategy. Podd advises companies to work with angel groups that have capital precommitted by Big Pharma. That commitment indicates an inherent interest in possibly acquiring technology that is developed or of acquiring the company. Individual groups are looking for specific types of companies that fit the strategic direction of the Big Pharma investor. As Podd stresses, "Strategic relationships are very important, and the presence of Big Pharma lessens the risk."

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Novel Financing For Gene Therapy Company

CATHY YARBROUGH Contributing Editor
@sciencematter

Gene therapy pioneer Katherine High, M.D., was looking forward to her first meeting in 2011 with Jeffrey Marrazzo, then a consultant to the CEO of Children's Hospital of Philadelphia (CHOP). A veteran of three life sciences companies, Marrazzo was meeting with Dr. High and other CHOP leaders to identify potential new revenue streams for the hospital.

Dr. High, an international leader in gene therapy research and clinical application, had considered postponing the meeting because she was so busy with her work as director of the hospital's Center for Cellular and Molecular Therapeutics (CCMT). However, she did not reschedule because she wanted to ask Marrazzo for a favor: Could he speak with the VCs who were calling her and inquiring about investing in CCMT's work on RPE65?

"I hadn't spoken to them yet, because at the time I was busier than usual with my patient care, research, and teaching responsibilities. In addition, VCs are not a constituency that I normally deal with," said Dr. High, professor of pediatrics at the University of Pennsylvania as well as a Howard Hughes medical investigator.

Scheduled to last just 60 minutes, Dr. High's first meeting with Marrazzo stretched to seven hours and was followed by many more meetings to determine the best approach for advancing CCMT's gene therapy discoveries. The result was a commitment of $50 million from CHOP to fund a new biotech company, Spark Therapeutics, to design, evaluate, and commercialize gene therapies for disorders that can lead to blindness, hemophilia, and neurodegenerative diseases. The company, like the hospital, is headquartered in Philadelphia.

CHOP's serving as the sole equity investor in Spark is "definitely a novel financing model for early corporate activities to develop novel therapeutics," said Marrazzo, now president, CEO, and cofounder of Spark. "Every situation is unique, and the situation should dictate the model."

Spark's situation was unusual because long before the company's official launch in late 2013, "many assets were already in place," said Marrazzo, who uncovered them during his seven-hour conversation with Dr. High. "It was like peeling back the layers of an onion, with each layer representing another asset," he said.

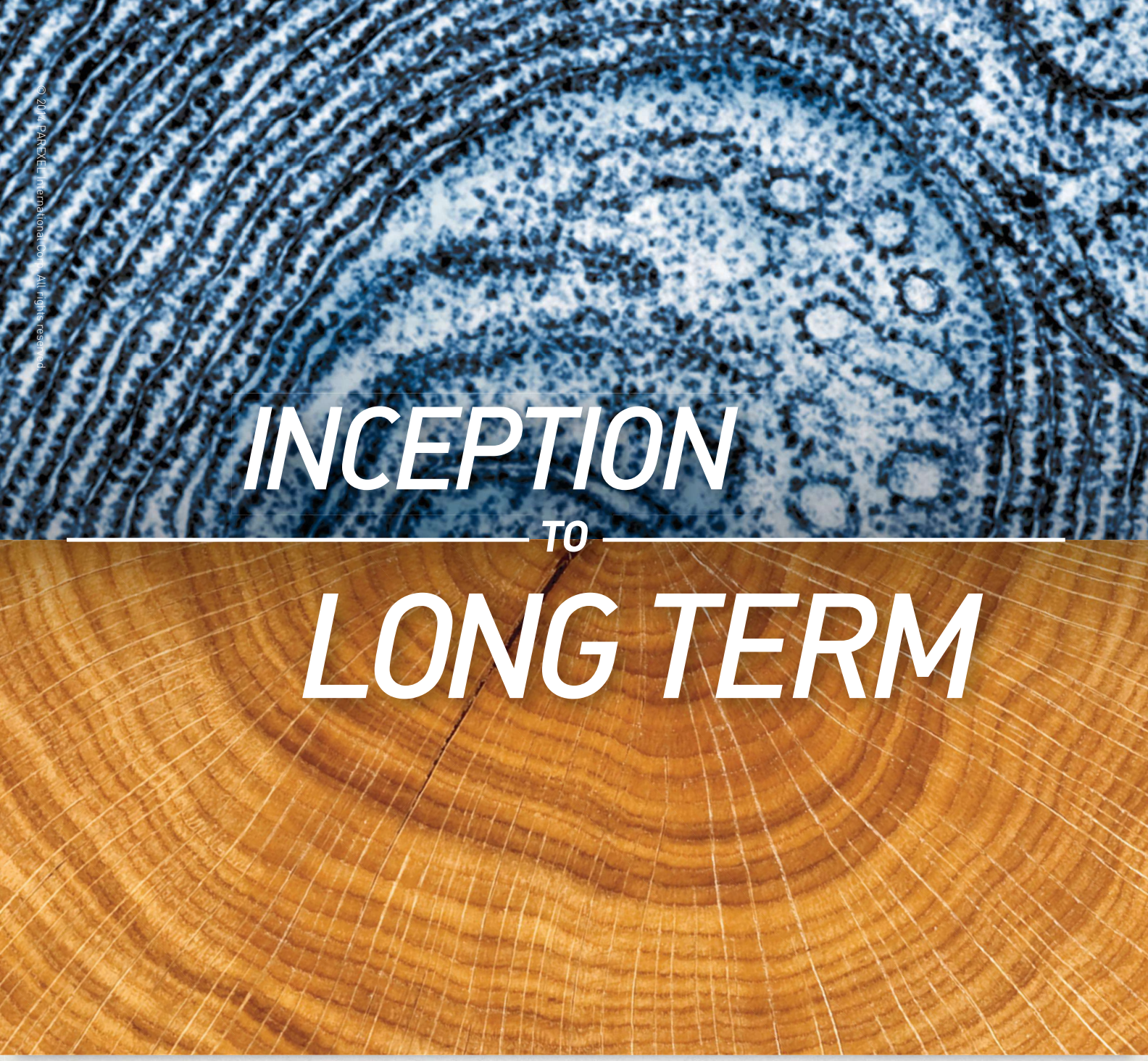
The assets included two clinical trials, a Phase 3 trial to treat a rare form of hereditary blindness, and a Phase 1/2 trial targeting hemophilia B, as well as staff members with gene therapy expertise in regulatory affairs, clinical research, and the manufacture of clinical grade vectors to transport genetic material into targeted cells.

"Assembled at the center were world experts in gene therapy," said Marrazzo. "CHOP had been incubating a biotech company within its four walls."

GENE THERAPY ASSETS UNDERVALUED

Before investing $50 million to launch and operate Spark Therapeutics, CHOP officials considered but ruled out a licensing deal with an existing biopharm company or a start-up with VC funding. "While we did have licensing deals on the table, that route would not have recognized the value of the asset in part because of the broad retrenchment that had occurred in the industry after the tragic 1999 death of Jesse Gelsinger in a gene therapy clinical trial," said Dr. High. Gelsinger died while participating in a clinical trial conducted by a University of Pennsylvania lab not connected to CCMT or CHOP.

Gelsinger's death and the clinical trial itself generated massive negative media coverage and concern about the safety of gene therapy from the NIH, FDA, and



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other scientific and medical organizations. As a result, funding for gene therapy R&D took a nosedive, and many companies and academic labs discontinued or significantly reduced their programs.

Dr. High, however, was one of the few scientists who did not give up on the promise of gene therapy. She staffed CCMT with many former industry leaders in the field who are now part of Spark's leadership team. CCMT and other labs continued their research to improve gene therapy's safety and ability to target specific tissues in the body. Their research advances have renewed the industry's interest in gene therapy. Novartis, Baxter, Celgene, and Biogene are investing resources in gene therapy, and several biotech companies also have been created. In addition to Spark, they include bluebird bio, Editas Medicine, GenSight, Lysogene, uniQure BV, and Voyager Therapeutics.

Although uniQure was the first company to receive regulatory approval from the European Medicines Agency (EMA) for a gene therapy product, Marrazzo said that he and his colleagues believe that Spark will be the first to receive the FDA's approval to market a gene therapy. In 2015, Spark will conclude its Phase 3 trial on forms of blindness caused by RPE65 mutations. UniQure has announced that it plans to submit a biologics license application (BLA) to the FDA for its gene therapy, Glybera, for the treatment of patients with a rare metabolic disorder that causes inflammation of the pancreas.

"I hadn't spoken to [VCs] yet, because at the time I was busier than usual with my patient care, research, and teaching responsibilities."

KATHERINE HIGH M.D.
Cofounder of Spark Therapeutics

Among the start-up companies, Spark and Voyager Therapeutics are the only spin-offs of academic, nonprofit organizations. Voyager's parent is the University of Massachusetts Medical School in Worcester. However, unlike Spark, Voyager is supported by VC funding.

Marrazzo predicted that more nonprofit organizations, including universities and research institutes, will establish commercial enterprises similar to Spark. "These nonprofits could look increasingly less like they have in the past and more like hybrids, and this is something that the industry will have to react to," he said.

"The Spark model creates an alternative to licensing and sponsored research for not-for-profit (NFP) organizations seeking to commercialize their discoveries," said Marrazzo. "As such, for the Big Pharma and Big Biotech companies as well as VC firms that have benefited from accessing NFP research at a discount, they will need to understand and embrace the model of NFP company incubation, formation, and financing and identify ways to participate. If the big companies choose to embrace the Spark model, there will be opportunity for partnership and joint value creation rather than competition."

"The Spark model creates an alternative to licensing and sponsored research for not-for-profit (NFP) organizations seeking to commercialize their discoveries."

JEFFREY MARRAZZO
President, CEO, and Cofounder of Spark Therapeutics

HOSPITAL'S FUNDING SUFFICIENT FOR COMMERCIAL LAUNCH

"An exit strategy that would require Spark to be acquired by a larger enterprise is not on the agenda of the company's board," said Marrazzo. "Our goal is to develop into a fully integrated, sustainable biopharmaceutical company specializing in gene therapy," he said. "We want to be in position to develop as many products as possible to treat both children and adults with debilitating genetic diseases. We can best serve the initial vision of CHOP if we make gene therapy a regular part of patient care."

To help guide Spark's evolution, two life sciences industry veterans have joined the company's board. They are Elliott Sigal, M.D., Ph.D., director, executive VP, CSO, and president of R&D at Bristol-Myers Squibb until 2013, and Rogério Vivaldi, M.D., CEO and president of Minerva Neurosciences, Inc., and previously the senior VP and head of the rare diseases business unit at Genzyme, a Sanofi company.

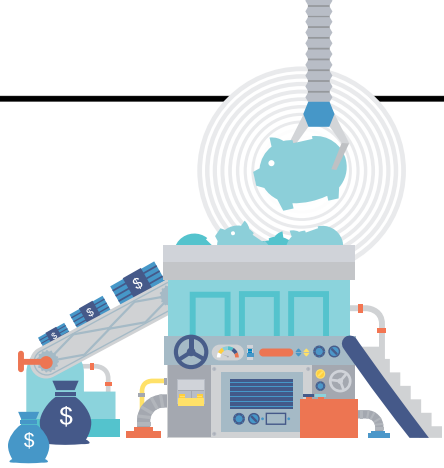
Anticipating that the FDA will approve its lead product, Spark is hiring staff to support the commercial launch of its gene therapy for RPE65 gene mutations blindness. "The challenges of managing and growing Spark do not significantly

differ from other new biotech companies," said Marrazzo, who previously held senior leadership positions at Generation Health, Tengion, and Molecular Health, Inc. Chairing Spark's seven-member board is a representative of CHOP, CEO Steven Altschuler, M.D. Also on the Spark board is Thomas Todorow, C.P.A., MBA, executive VP for corporate services and CFO of CHOP.

Many of CCMT's assets, such as the two clinical trials and many members of its leadership, are now at Spark. Another company asset is Spark's exclusive license from CHOP to commercialize the center's proprietary manufacturing technology. For its preclinical studies and clinical trials, Spark will be able to use clinical-grade gene therapy vectors produced by the center's state of the art cGMP clinical facility. "We view CHOP as our technology partner as well as investor," said Marrazzo.

In January 2014, Spark completed patient enrollment in its Phase 3 study of CCMT's novel gene therapy. In the therapy, a vector carrying a normal copy of the gene is inserted behind the retina of the patient's eye. The Phase 3 trial builds on CCMT's successful Phase 1/2 clinical trial of 12 patients with Leber's congenital amaurosis whose vision measurably improved after the gene therapy, said Dr. High, a cofounder of Spark and a scientific adviser to the company. Before the trial, several of the children were profoundly blind. As a result of the gene therapy, they were able to recognize faces and walk without the aid of a cane or a companion. The children's vision improved so much that they no longer had to depend on Braille to read.

If the Phase 3 trial also shows that the gene therapy is safe and effective, the hospital's funding will underwrite Spark's preparation and submission of a BLA and the commercial launch of the product. "If FDA approves the BLA, Spark has the resources to generate first revenues," said Marrazzo.



Marrazzo said that he expects that the hospital will continue to be an investor in Spark, but it will be opportunistic. "If the Spark board decides to expand or expedite our strategy, we may seek other investors or partners," he concluded. L

A Tough Lesson On The Road To Commercialization

FRED OLDS Contributing Editor

How do researchers determine their science is worth taking to translational research and commercialization? Good science alone is not enough. The challenges of funding, competition, and regulatory hurdles crush many endeavors. Entrepreneurs find that commercialization starts with good data but requires developing networks, precise planning, building an experienced team, and perseverance.

Mike Sherman, CFO at Endocyte Inc., says, "Some endeavors get started without an understanding of the real world. I don't know how many interesting ideas I've heard that fall down on one of three elements: solving a problem that physicians don't see as a problem, creating a solution that will be made obsolete by a competitive alternative that was ahead in the game, or an unclear path on how you would get approval."

Sherman says the core team has to make a frank assessment of the discovery. Based on seeing the preclinical evidence, does it makes sense that the science should work in humans? Is there specificity for the targets? Does this discovery bring a meaningful advantage over current treatments? Is this a breakthrough or just a bit of new knowledge? If the determination on the science is positive, the assessment then becomes one of business. The process to commercialization goes in steps. So the team has to evaluate its prospects for each of those steps to determine if they have the necessary resources and perseverance. Choosing a viable platform for development is part science and part business.

IT STARTS WITH NOVEL SCIENCE

One easy answer on whether to proceed to a start-up is investor buy-in. Venture capitalists look for "interesting science" that provides a significant advantage in treating an important human disease. Their support is an explicit endorsement of the science. "When you publish a series of articles showing innovative science, it's amazing how venture capital firms contact you and say, 'Let's start a company,'" says Sherman.

The "interesting science" for Endocyte is its small molecule drug conjugate (SMDC) technology, which provides targeted delivery of drug payloads to diseased cells and a companion imaging agent that helps identify patients most likely to benefit from SMDC therapy. The technology is based on the research of Purdue professor and chief science officer at Endocyte, Philip Low, Ph.D. and Chris Leamon, Ph.D., vice president of research at Endocyte. Leamon says, "It's a Trojan horse approach. We target the disease and bypass healthy cells."

Endocyte uses small molecular weight ligands to carry drug payloads to targeted cells. Initially the company focused on folate receptors, which are highly expressed on certain cancer cells, but not appreciably on healthy cells. Endocyte has designed a linker construct to attach potent therapeutics to folate, creating an SMDC. When injected, the SMDCs perfuse quickly and bind to the folate receptors. The cancer cell takes up the folate and payload through endocytosis. Once in the cell, the linker releases the payload, which begins its activity in destroying the cancer cell.

But interesting science and good data don't assure buy-in. Without early VC backing, an entrepreneur has to carefully reassess the discovery to determine its impact on human health, rework a

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detailed business plan that may win investors' trust, and evaluate whether the core team has the stamina and resources to pursue a protracted campaign to get support. Venture capitalist Larry Lasky, Ph.D., a partner at U.S. Venture Partners, says, "Good science always bubbles to the top." It may just take longer and require perseverance, especially if one challenges current accepted knowledge or lacks standing in the scientific community.

Ingmar Hoerr, Ph.D., MBA, cofounder and CEO of CureVac GmbH, says he was met with skepticism when he attempted to get support for his research in mRNA (messenger ribonucleic acid), which CureVac is now developing as an entirely new class of therapeutics. In the late 1990s when then-Ph.D. candidate Hoerr was conducting experiments in gene therapy, accepted thought assumed that mRNA was too unstable to last long enough to effect a T-cell immune response. Unexpectedly, the immune response in his experiment was greater with mRNA than the test compound. Hoerr says, "I thought I had failed completely." He repeated the experiment, taking even greater care and got the same results.

His research was met with suspicion and doubt. He asked himself, "What should I do now? Nobody believes me." He did find, however, a believer with complementary skills in his lab research partner and Ph.D. candidate Florian von der Mülbe, now COO at CureVac. The two started a company and shopped their research around German VCs without success. Hoerr says, "We were Ph.D. candidates, 30 and 31 years old. We were so naive. We told the investors we had discovered this new biomolecular activity and had great results from our experiments." Investors were not sold.

PERSEVERANCE

Based on the results of their work, Hoerr and von der Mülbe determined that mRNA was worth the effort to bring to market. They found that mRNA could be designed to induce an immune response that would target specific diseased cells. When injected, mRNA would be taken up by cells, recognized as antigenic, and trigger a precise immune response against the target disease. "You have to believe your science. We were living it. We believed it. None of the experiments were failing." He and von der Mülbe returned to the university and continued to build data using grants and an investment from the VC firm Leonardo Venture.

With help from the city of Tübingen in the form of a €3 million ($4,117,317 U.S.) GMP lab facility, Hoerr took the company off-campus to continue development. 2003 to 2005 began what Hoerr describes as a very dark period; the company ran out of money. To stay afloat, they decided to manufacture and sell RNA. This not only provided cash flow, it gave them valuable expertise in manipulating and coding RNA.

NETWORKS PROVIDE INFORMATION, CONTACTS, AND SUPPORT

Networks offer more opportunities for feedback to analyze the value of a discovery. A company can learn about current research that might support its concept or lead to competitive products. The larger a network, the fewer the degrees of separation from contacts that can offer backing or resources.

Hoerr says early on he felt the road to market was all about the data, that the science would sell the VCs. "Which was wrong, of course," he says. "It's about everything. You have to be trusted. You have to have a reputation. You need a network."

It was the network his company established through research and marketing RNA that finally got Hoerr in touch with Dietmar Hopp, the founder of SAP. He says, "It was the first time I was not in front of another researcher, VC, or banker. Here was contact with an entrepreneur. I told him we had a GMP facility. We were seeking regulatory advice. We had RNA and animal results. The only thing we didn't have was money." Hopp backed the company. It was that connection created through their network that garnered the funding to grow CureVac into an independent biotech.

Sherman says Endocyte had a network Dr. Low had established through his career. Low knew researchers in biochemistry and oncology and stayed in contact with the pharma industry. He was able to assess Endocyte's science and predict it would be first in that space and successful. Targeted drug delivery with reduced side effects is very attractive, and his contacts provided the groundwork to seek partners in development and research.

IS THERE A CLEAR PATH TO REGULATORY APPROVAL?

The final critical analysis is whether the team feels they have a clear path

"When you publish a series of articles showing innovative science, it's amazing how venture capital firms contact you and say, 'Let's start a company.'"

MIKE SHERMAN
CFO of Endocyte Inc.

"I told him we had a GMP facility. We were seeking regulatory advice. We had RNA and animal results. The only thing we didn't have was money."

INGMAR HOERR, Ph.D., MBA
Cofounder and CEO of CureVac GmbH

to approval by regulatory agencies and acceptance by payers. Sherman says, "If you're breaking ground in new pathways or where the regulatory path is not well-defined, there are challenges."

New science doesn't necessarily pose a barrier to approval. CureVac is in clinical trials with its mRNA technology to treat lung and prostate cancers, and they are conducting studies in prophylactic vaccines. Although mRNA technology is a new class of therapeutics, it is being applied in a known space. Cancer has an established path to approval, and the technology can be measured using current protocols and outcomes. Endocyte found that its technology was actually perceived as an advantage, because its companion imaging can predict which patients are most likely to benefit from the therapy.

ADVICE FROM LESSONS LEARNED

Determining whether a discovery can be commercialized begins with realistic analyses of all the steps to production, not just the science. Networks can provide additional thoughts on the viability of starting a company, but the empiric evidence comes when the endeavor receives financial backing.

Hoerr says, "The process to bring a product to market is not just about the science and research. It's about humans, about a story." The data is most important, but an entrepreneur needs to translate the science into a context that explains why the discovery is important, then inspire others to support the translational research and commercialization.

Leamon recommends starting with a passion for your work and staying connected to the patient. Knowing what the patient suffers helps you evaluate whether your discovery answers an important problem in the human condition and advances medicine.

The MINT Countries: Building On The BRICs

SUZANNE ELVIDGE Contributing Editor
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Back in 2001, Jim O'Neill, previously the chair of Goldman Sachs Asset Management, coined the acronym BRIC (Brazil, Russia, India, and China) to describe four up-and-coming economies. In 2013 a new acronym emerged — MINT (Mexico, Indonesia, Nigeria, and Turkey).

This article will introduce the MINT countries and take a brief look at the biopharma industry in each region, with a particular focus on Mexico and Turkey, the largest economies of the four.

O'Neill has selected the MINT countries as potential top 10 global economies by 2050 based on the observation that all four have young populations (see Table 1) and what he describes as "favorable demographics."

Of the four, Indonesia has the largest population, but Nigeria is growing fast, with the highest fertility rate and rate of natural increase and the largest population of children age 15 years and younger. By 2050, Nigeria's population is projected to outstrip that of the other three MINT countries and could by then be the fourth most-populous country in the world, with a population of 402 million. While pharmaceutical market size is partly driven by population numbers, the major driver of market size is the GDP of a country, as individuals and countries both have more disposable income to spend on healthcare (see Figure 1).

Of the four countries, Nigeria and Indonesia have the fastest and most consistently growing GDP, at around 6 to 8 percent. However, these two countries have the lowest GDPs of the four MINT countries, at $1,555 and $3,557 per capita respectively, compared with $9,749 in Mexico, $10,666 in Turkey, and $51,749 in the United States (2012 figures from the World Bank).

Nigeria's growth has been driven by oil prices. However, political unrest in neighboring countries could affect Nigeria's economic future and its attractiveness as a place for investment. The growth rates of GDP in Turkey, Mexico, and the United States were all affected by the financial crisis of 2007 to 2008. After fast growth in 2010 and 2011, Turkey's GDP was hit again in 2012 by the country's political and financial troubles. In its World Economic Outlook, published in October 2013, the IMF (International Monetary Fund) predicted that Turkey's economy will grow again, albeit slowly. In the same report, Mexico's growth rate was expected to slow to 1.25 percent in 2013, but return to 3 percent in 2014, growing to 3.5 to 4 percent in the medium term.

MOVING INTO MEXICO

According to consultancy and executive search experts Russell Reynolds Associates, Mexico's pharmaceutical industry is worth around $11 billion and is the 11th largest pharma market worldwide. About 50 percent of pharmaceutical sales (by unit) are to the public sector.

There have been some major changes to the Mexican pharmaceutical industry in the past decade. Until 2008, companies selling drugs in Mexico had to have a manufacturing plant in the country. As Jaime Padilla, a consultant at Russell Reynolds Associates in Mexico City and a pharmaceutical industry specialist, explained, this was part of a scheme to industrialize the country.

The Mexican government changed this policy in 2008, but it left a significant manufacturing infrastructure in place that could be exploited to grow the domestic pharma industry. This included plants, logistics, regulatory structures, and an experienced talent pool. The government is also moving toward cutting red tape and aligning its regulatory authority, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS), to the International Conference on Harmonization (ICH) guidelines. While Mexico was relatively late adopting generics, now around 60 percent of unit sales are generic drugs, and a large proportion of the domestic players are producing generics.

"Most of the top 20 to 25 pharma companies have plants in Mexico, but recent growth has been through local and multinational generics players," says Padilla.

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"There is some innovation, but it mostly involves doing new things with available drugs, for example, combinations of drugs in a single pill tailored for a local market. I expect to see growth in the number of studies carried out in Mexico rather than seeing an increase in innovation."

Mexico has not always been a top 10 market for individual drugs in terms of revenue, as Padilla explains, but he expects to see this change for some segments. For example, diabetes is a sizable market and probably will be the biggest public health issue in Mexico in the coming years. Mexico's population is sizable at around 116 million people. Currently the population is relatively young, which means in 10 to 15 years there will be a greater need for healthcare services. Also, considering the country's GDP is growing and healthcare coverage is increasing, Mexico should become a key potential market for companies both outside and inside the region. "The companies that understand these changes and know how to negotiate with the government and work closely with the retail channels and the patients will be the ones that succeed," says Padilla.

A TAKE ON TURKEY

Geographically, Turkey occupies an interesting location, on the edges of Europe and the Middle East. The medical needs in Turkey are similar to those in the rest of Europe where cancer and cardiovascular disease are common. Hepatitis B and hepatitis C are also prevalent in parts of the country.

"The Turkish pharmaceutical industry is mostly based on marketing and manufacturing, and there is not much focus on drug discovery," says Hesna Yiğit, of Adıyaman University in Turkey (previously the associate director of preclinical pharmacology at Oculus Innovative Sciences and a research investigator at Bristol-Myers Squibb). "These are mostly international rather than domestic companies," she added.

The Turkish pharma industry spent around $59.2 million (€43 million) on R&D in 2011 compared with around $7.7 million (€5.5 billion) in the U.K. and around $7.3 billion (€5.3 billion) in Germany. The Turkish government is attempting to turn this around, however, perhaps driven by the trend of outsourced manufacturing away from the country. According to the Vision 2023 strategy document from the Turkish Association of Research-Based Companies (AiFD), the Turkish government plans to move the country into the top 10 economies in health services by 2023. It will do this by increasing R&D expenditure to 3 percent of GDP and by increasing health-related exports to $500 billion. This move will be supported by the return home of Turkish ex-pats.

"There are more and more Turkish scientists who have worked in U.S. and European pharmaceutical companies who are moving back to Turkey and bringing experience, contacts, and networks with them," says Yiğit. "These people could help to create collaborations with companies outside of Turkey."

This move toward innovation also is supported by academia in Turkey. As an example, Yiğit is currently working on a project supported by TÜBİTAK (Scientific and Technological Research Council of Turkey) at Adıyaman University. The project involves screening plant extracts from the Adıyaman region for antibacterial and antiviral activities. She is also working with the chemistry department to screen synthetic compounds for antimicrobial activity.

INSIGHT INTO INDONESIA

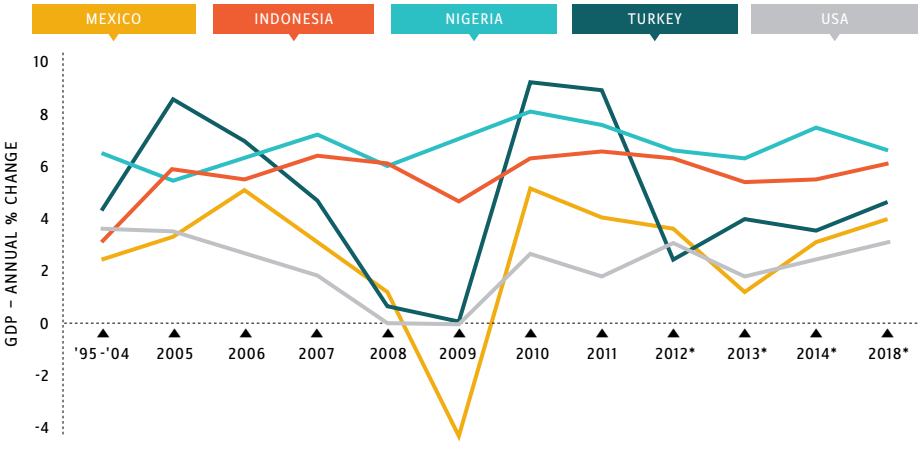
According to a report from the consulting company Pacific Bridge Medical, the Indonesian pharmaceutical industry is worth around $5 billion, and pharmaceutical spending is increasing per capita. Around three-quarters of the pharmaceutical companies in Indonesia are domestic, and while the country represents a growing potential market, there are restrictions. Namely, companies that sell drugs in Indonesia must manufacture them locally, and domestic companies can have a maximum of 75 percent foreign ownership. However, there are signs that these rules are beginning to be relaxed.

NEWS ON NIGERIA

The Nigeria pharma sector is worth about $3 billion, according to Bunmi Olaopa, chair of the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN). Nigerian manufacturers produce around 65 percent of the medicines and healthcare products made in the Economic Community of West African States (ECOWAS). Members of PMG-MAN have invested nearly $44 million to improve manufacturing practices and expand factories.

The WHO prequalification program

FIGURE 1 ANNUAL PERCENTAGE CHANGE OF GDP



Source: IMF (International Monetary Fund) World Economic Outlook 2013 / *Projected data / United States included for reference

TABLE 1 POPULATION IN THE MINT COUNTRIES

	MEXICO	INDONESIA	NIGERIA	TURKEY	USA
POPULATION (MILLIONS)					
2012	116.1	241.0	170.1	74.9	313.9
2025	131.0	273.2	234.4	85.4	351.4
2050	143.9	309.4	402.4	93.2	422.6
FERTILITY RATE	2.3	2.3	5.6	2.0	1.9
RATE OF NATURAL INCREASE (%)	1.5	1.3	2.6	1.2	0.5
% POPULATION (<15 / >65)	29 / 6	27 / 6	44 / 3	26 / 7	20 / 13
GNI PPP PER CAPITA (US$)	14,400	4,200	2,240	15,530	2,240

Source: IMF (International Monetary Fund) World Economic Outlook 2013 / United States included for reference
GNI – gross national income; PPP – purchasing power parity

aims to make medications available for those in need, and Nigeria is working toward this prequalification. In an interview with Nigerian newspaper the *Daily Independent,* Paul Orhii, director-general of the National Agency for Food and Drugs Administration and Control (NAFDAC), said that he expects significant growth in the drug manufacturing sector, and the WHO prequalification will boost growth. Olaopa hopes that up to five Nigerian manufacturers could have products prequalified during 2014.

According to IMF figures, 2.9 percent of the male population and 4.4 percent of the female population aged 15 to 49 have been diagnosed with HIV/AIDS. This major unmet medical need is a crucial target both for the pharmaceutical industry and for charitable and philanthropic support. L

Driving The Innovation Agenda: The Case Of Ontario, Canada

REZA MORIDI

Continued discovery is the lifeblood of the life sciences sector. As researchers across the globe race to find the next disruptive treatment or technology, government has a critical role to play in creating the conditions for innovation to flourish.

Innovation thrives at the intersection of industry and government investments, government policy and regulation, and academic or institutional research. Innovations are often the result of careful planning, cooperation, and investment across all three sectors.

Strong government action has helped forge an innovative life sciences cluster in Ontario, Canada. Across the province, publicly funded research institutions are investigating promising new biomedical technologies, training young scientists, and working with industry partners. In Ontario, more than 100,000 researchers work on issues ranging from life-saving vaccines to robotic software and climate-change mitigation. Companies in Ontario have access to a wide range of government programs that can help accelerate growth and new-product development. The province also makes innovation affordable for industries through its R&D tax incentive program, which is available to qualified businesses of any size and applies to a range of eligible costs that is broader than in the U.S. and many other countries.

EXAMPLES OF GOVERNMENT-LED COLLABORATION

Ontario Centres of Excellence (OCE) is a prime example of how government-led collaboration can have a direct impact on innovation. Before OCE was incorporated in 2004 and brought numerous sector-specific centres of excellence under one roof, collaboration between universities, colleges, research hospitals, and industry was limited. Consensus was that these academic and research institutions were producing quality research that was not being used to its full potential by industry. The core strength of OCE is its ability to bring academia and industry together as prospective partners and turn ideas into income. OCE co-invests alongside its industry partners to commercialize innovation originating in the province's publicly funded colleges, universities, and research hospitals in the segments of the economy that will drive Ontario's future prosperity and global competitiveness, such as advanced health technologies. Fueled by government, OCE is a key partner in delivering Ontario's Innovation Agenda.

Another example of Ontario's industry collaboration is MaRS Innovation, a highly specialized commercialization hub based in Toronto. MaRS Innovation was designed to accelerate the path to market for great research ideas. At the time of its inception, MaRS Innovation was completely unprecedented and spoke to the readiness of the academic, healthcare, and research communities in Ontario to unleash the benefits of clustering. This willingness to experiment has enabled MaRS Innovation to bundle research assets together, from both a scientific and business perspective, while keeping the individual integrity of the intellectual property intact.

MaRS also supports life sciences innovation and commercialization through Excellence in Clinical Innovation and Technology Evaluation (EXCITE). EXCITE is a collaboration between a range of stakeholders in the health technology sector. It was created to harmonize health technology evaluation into a single, premarket, evidence-based evaluation process for innovations with disruptive potential and specific relevance to health system priorities. EXCITE evaluates medical technologies in the premarket phase of development, and this contextual evidence can both align industrial technology innovation with health system demands and improve the quality and relevance of technologies still in development. It also helps streamline adoption by the healthcare system, resulting in lower healthcare costs and increased patient benefits.

THE BENEFITS OF ONTARIO'S LIFE SCIENCES CLUSTER

In addition to EXCITE, Ontario's life sciences cluster also benefits from the

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Health Technology Exchange (HTX). HTX manages a $21.4 million fund on behalf of the Ontario government to finance emerging and established Ontario-based companies to develop, produce, and commercialize innovative market-leading advanced health technologies. Since 2011, HTX has approved 26 projects for funding, investing $9.8 million into public/private commercialization projects worth $46 million. Ontario's investment in the HTX has also fostered the creation of more than 200 jobs.

Another innovation driver for Ontario is the Voucher for Industry Association (VIA) R&D Challenge, part of Ontario's Collaboration Voucher Program. VIA connects industry associations or groups of companies with Ontario's publicly funded academic research institutions to address sectorwide research and development challenges. VIA projects focus on challenges identified by an industry sector where business solutions have demonstrable global market potential. Project outcomes include commercialization and increased productivity with significant economic impact for Ontario and program partners. Companies may use research results to their own and/or their supply chain's commercial advantage.

HEALTHCARE INNOVATION/ COLLABORATION SUCCESS STORIES

Beyond the desire to improve productivity, a more tangible and immediate benefit of innovation is the ability to solve challenges in healthcare. Both practitioners and policy makers are looking for new technologies to help solve critical, worldwide healthcare challenges. Rising healthcare costs are one of the most critical issues. Many jurisdictions are implementing programs directed toward gaining efficiencies and constraining cost escalation. Ontario is no different. Many Ontario-based start-ups are focused on developing portable, affordable diagnostic devices designed to keep healthcare costs down.

A few of these promising innovations include ApneaDx Inc., an at-home sleep monitoring system, and Otosim, a medical training simulator that dramatically improves diagnostic accuracy rates.

Prior to the introduction of ApneaDx in 2012, spending a night in a sleep lab (polysomnography) was the gold-standard for diagnosing sleep apnea. ApneaDx addresses the market need for a clinical-quality sleep apnea monitoring system that can be easily used by patients at home. ApneaDx provides sleep-lab-quality data with minimal inconvenience (e.g. no wires, bulky equipment, cumbersome setup, etc.). The device will cost a fraction of the price of a sleep lab visit or other home monitoring systems. ApneaDx obtained EXCITE premarket evaluation in 2013 and has successfully raised $500,000 in seed funding from MaRS Innovation, the Ontario Brain Institute, and Johnson & Johnson.

For years, general practitioners and pediatricians have used an otoscope to screen for illness in the outer and middle ear. However, diagnostic accuracy with this tool is typically less than 50 percent. Enter OtoSim. The OtoSim system is for training medical students and involves a small simulator unit with an opening that resembles a life-sized human ear canal. The ear form has a realistic feel and shape. The student uses a traditional otoscope to look inside the unit where images of ear canals and tympanic membranes (ear drums) are displayed. The instructor's laptop or desktop computer, which is connected to the OtoSim unit via a USB cable, holds a library with hundreds of images of common ear pathologies. The key to OtoSim's training success is that it enables the instructor and medical student to simultaneously review the same images. The instructor monitors what the student is seeing and is able to provide specific directions and feedback.

In the less than two years since OtoSim was launched, hospitals and medical schools in more than a dozen countries have snapped up these training units. OtoSim's rapid worldwide acceptance can be traced back to investment and support from MaRS Innovation.

Not all innovations are inexpensive, but some can be life-changing. For example, for the estimated 187 million people worldwide who live with low vision, eSight is truly life-changing. A new class of wearable assistive technology, eSight, is helping the blind to see. For some, it means being able to read a book or watch a sporting event for the first time in years. For others, it opens new job opportunities. The eSight system has two lightweight components: a headset and a controller. In the headset, a forward-pointing, high-resolution video camera sends a signal to the controller. An algorithm converts the data to match the wearer's preferences, and the signal is sent back to LED displays on the inner surface of the headset.

To develop eSight, the founder assembled a team of leading experts from both the medical and engineering worlds. The team benefitted greatly from being located in Ottawa, known as "Silicon Valley North" as it is home to numerous high-tech companies. It is also home to one of Canada's top research centres in ophthalmology, the Eye Institute at the Ottawa Hospital Research Institute, which was brought in early in eSight's development.

Over the past few years, eSight's radical new vision technology was developed and refined with the help of experts from the Canadian National Institute for the Blind, the University of Waterloo's School of Vision, Lighthouse International, the Massachusetts Eye and Ear Infirmary, and many others. The wearable assistive device is licensed by both Health Canada and the U.S. FDA. It has generated interest from as far away as South America and the Middle East.

Ontario has worked hard to create the conditions where we can capture lightning in a bottle and bring exciting new medical advances to the rest of the world. It is a testament to the nearly unlimited potential of collaboration.

Reza Moridi is Minister of Research and Innovation for Ontario, Canada. He is an award-winning scientist, engineer, educator, business leader, and community activist.

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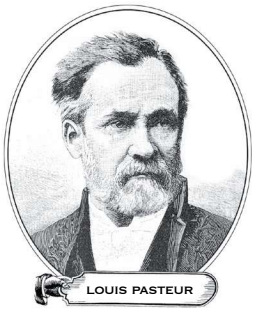

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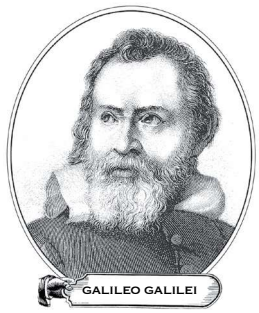

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JIM BURKE

Jim Burke is senior VP of contracting and pricing solutions at Alliance Life Sciences Consulting Group. Prior to joining Alliance in 2004, he was a director in I-many's Professional Services organization.

Financial accruals have become a major headache for corporate finance teams in the life sciences industry as they are increasingly difficult to manage and can lead to major business issues if calculated incorrectly. These accruals are an important part of compliance with generally accepted accounting principles (GAAP). Funds are set aside to cover the financial obligations associated with sales and from promotional programs, rebates, and discounts. They are hard to manage due to the fact that the data for each type of program is captured in different places within an organization. The data associated with co-pay programs, direct rebates, and chargebacks must be gathered, and then the amounts to set aside must be determined based on past and future projections.

The problem is that most companies don't have an automated way of pulling all the data together and calculating the appropriate accrual rate. Manufacturers do the calculations manually or in an offline tool. Depending on the company and the kinds of promotional programs it offers, calculations can range from the complex to the extremely complex.

Any calculation errors can have a significant impact. If the accrual percentage is too high for rebates and promotions, funds are essentially being taken away from other areas of the business, such as research and product development, which can help grow revenue. But if enough isn't reserved, manufacturers could find themselves in a cash crunch, and money will need to be borrowed to cover obligations. If the amounts get too large, it can also be considered a "material impact" item for earnings reports.

There's another aspect that companies are missing. Many organizations are spending more time and money on the mechanics of the accruals — the number crunching — than on understanding what the data is telling them. They're missing an opportunity to analyze the accruals to see what promotions and programs are really driving the business, helping them expand market share, and affecting revenue.

AUTOMATING THE ACCRUALS PROCESS

Most companies have a consistent set of issues to address. Compliance is first and foremost on everyone's mind. The accrual methodology has to align with GAAP, and then ultimately, a system should be in place that has the right process controls and audit capabilities. The methodology must be documented, i.e., how you came up with your calculations, and it must be reconcilable to your auditors. But the formula can't be static or locked down. The accrual rates need to evolve over time based on actual business results and sometimes may need to adjust to the rates in real time, so the process has to be flexible enough to accommodate human intervention.

The calculations may need to be adjusted when unforeseen events occur — shortages, business interruptions, and other unplanned circumstances. An example from the generics pharmaceutical world: Imagine that you are one of only three companies producing a certain compound. You learn that the FDA has shut down one of your competitor's plants, so you know that your sales are going to increase. If you have volume-dependent pricing or rebate programs that incorporate that product, you will need to increase your accrual rate to accommodate higher sales projections. It's an unpredicted circumstance, but you have to deal with it immediately.

KEY CONSIDERATIONS & RECOMMENDATIONS

Some of the key success factors are to consolidate the incentive program data into a central system, to apply systematic accrual rate calculations, and to evolve them based on real results over time. Depending on the situation, it might not be possible to automate 100 percent of the transactions, but it can still be valuable to automate as many as possible, while allowing the flexibility for human intervention when needed as a means of controlling the process without constraining it.

Finally, one shouldn't simply focus on getting the calculations right. Analyze the data to see which promotional programs are having the greatest impact on the results. Fine tune the mix of programs so that results are being continually optimized.

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What To Consider With A BYOD Approach To PRO Data Collection

CHAD GWALTNEY Ph.D.

Chad Gwaltney, Ph.D., is chief scientist and regulatory advisor, endpoints at ERT. He is a thought leader in the fields of pharmacotherapy and clinical outcome assessments and is widely published in addictive behaviors, cardiovascular health, and content validity of patient-reported measures.

Interest in the bring your own device (BYOD) approach to capturing electronic patient-reported outcomes (ePROs) is increasing dramatically among sponsors. With BYOD, patients use their own devices (smartphones, tablets, personal computers) to complete ePRO diary assessments, rather than separate, dedicated devices provided to them by the sponsor. BYOD approaches have notable strengths and can significantly reduce the time, effort, and costs associated with dedicated devices. However, while BYOD is emerging as a reliable and appropriate option for post-approval studies — where real-world data are critical, relatively large sample sizes may be used, and patients may be less likely to regularly visit a clinical site — there are a number of questions that sponsors should consider before using it in pre-approval (phases 2-3) research.

WHAT IMPACT WILL BYOD HAVE ON PATIENT RECRUITMENT? WILL IT LIMIT RECRUITMENT TO ONLY THOSE WHO OWN THESE PERSONAL DEVICES?

The seeming ubiquity of smartphones is a big reason for the appeal of BYOD. However, although smartphone penetration is increasing, many individuals still do not own them, and ownership is likely biased in ways that will impact a clinical trial (age, region, socioeconomic status).

WILL MIXING MODALITIES IN A SINGLE TRIAL AFFECT OUTCOMES?

Sponsors need to consider if/how enabling patients to use their own devices could affect their responses to PRO items. Also, there are potential scientific and regulatory concerns with the multiple interface differences that are certain to be present in a BYOD approach (e.g., device size, method of inputting responses, other functions available to user). BYOD approaches inherently introduce mixed modes of administration to a trial, and this could introduce unanticipated response biases. The nature of the modality used by patients may not be random; it may be tied to other factors that could influence responding. For example, in Web-based BYOD studies, some patients may be able to respond in any location at any time using a smartphone, while others using a desktop computer in their home may be limited in the timing and location of their entries. A unique feature of BYOD is that variability due to mixing modalities may not only cause response differences across patients using different devices, but also within the same patient, if they use different devices to respond to items in a single study.

WILL COMPLIANCE WITH THE ePRO PROTOCOL BE ADVERSELY IMPACTED BY BYOD APPROACHES?

Increased compliance is one of the key reasons why ePRO is essential in studies implementing patient diaries. The high rates of compliance with traditional ePRO (> 90 percent typically) are due, in part, to the alarm functionality that is included in most dedicated eDiary devices, typically via an audible alarm that cannot be muted. In a BYOD scenario that utilizes smartphones, ePRO apps can use reminders, but this alarm functionality can be limited by user preferences or through the operating system itself.

DO PATIENTS INTERPRET A PRO INSTRUMENT IMPLEMENTED VIA BYOD THE SAME WAY AS ITS INITIAL, PAPER-AND-PENCIL FORMAT?

The FDA's PRO Guidance states, "When a PRO instrument is modified, sponsors generally should provide evidence to confirm the new instrument's adequacy." This includes changing an instrument from a paper to electronic format. The challenge with BYOD is that there are a number of possible electronic platforms that could be used by patients, each with different screen sizes and other interface features. It is difficult at the outset of a trial to ensure that patients will interpret the electronic administration the same way across all potential device options. This could lead to scientific and regulatory concerns about the integrity of the data collected through BYOD approaches.

A BYOD approach to ePRO data collection offers significant benefits in clinical research. Its use in post-approval studies — which have different logistic characteristics and scientific goals — can provide important data to sponsors in a more cost-effective manner than dedicated, handheld eDiaries. However, additional research is needed to demonstrate that patients comply with and interpret PRO instruments in the same way across different types of personal devices.

like mapping the genome was more than a science project

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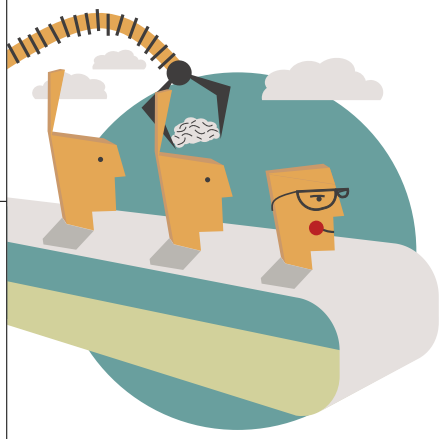

Stop Outsourcing Your Change

JUSTIN WASSERMAN

A few years ago I worked with a multinational pharmaceutical firm whose new CEO was looking to dramatically transform the business. The company was overly complex and slow-moving and lacked strategic alignment around its resource allocation. He knew things needed to change, so he did what countless other executives have done in similar situations — relied on an army of internal (six sigma) and external consultants.

He didn't know it at the time, but this did more harm than good.

Why? Bringing in "experts" to lead the change process meant leadership could abdicate their change responsibilities. The foreign "consultant-speak" of the "change experts" created more confusion than clarity and caused employees to lose sight of the goals the company had set out to accomplish. Time after time, the company's change initiatives fell flat because employees' heads and hearts just weren't in support of the changes.

I've seen this scenario occur countless times. But I've also witnessed organizations undergo major transformations successfully. The difference? Successful companies in-source their change.

Justin Wasserman is an engagement leader at Kotter International, a firm that helps leaders to accelerate strategy implementation in their organizations.

IN-SOURCING CHANGE

Change should be a fundamental skill in all companies — one that can be unlocked by looking within. Within every organization lies a hidden capacity of talent that must be tapped. Trusting your employees with this responsibility can seem daunting, but I've seen four building blocks of in-sourcing that ease the process:

1 **Urgency**: The first (and most important) step is to build urgency with your employees around a critical make-or-break opportunity. Don't just tell your employees that "X" is bad and needs to be fixed. Position the change as a big opportunity and in a way that captures the hearts and minds of your people to help propel you to new heights.

2 **Representation**: Involving employees in the change process is not about assembling your go-to "A-team" of executives and high-potentials. It's far more effective to create the conditions for choice — a "get to" rather than "have to" environment — by giving employees of all levels the chance to volunteer. You'll be surprised how many hands get raised.

3 **Volume :** As a rule, at least 50 percent of your organization should be helping drive the change process. If employees are in support of opportunity and feel like you genuinely want their help, they will volunteer their discretionary time.

4 **Duration**: Even if you have thousands of excited employees from all levels of your organization working to make a major strategic shift, you will fail if you declare victory too soon. Even when it looks like you've successfully seized your big opportunity, don't let up until the change has been anchored into your culture. But don't forget to celebrate the small wins throughout the process, well before you reach the finish line. L

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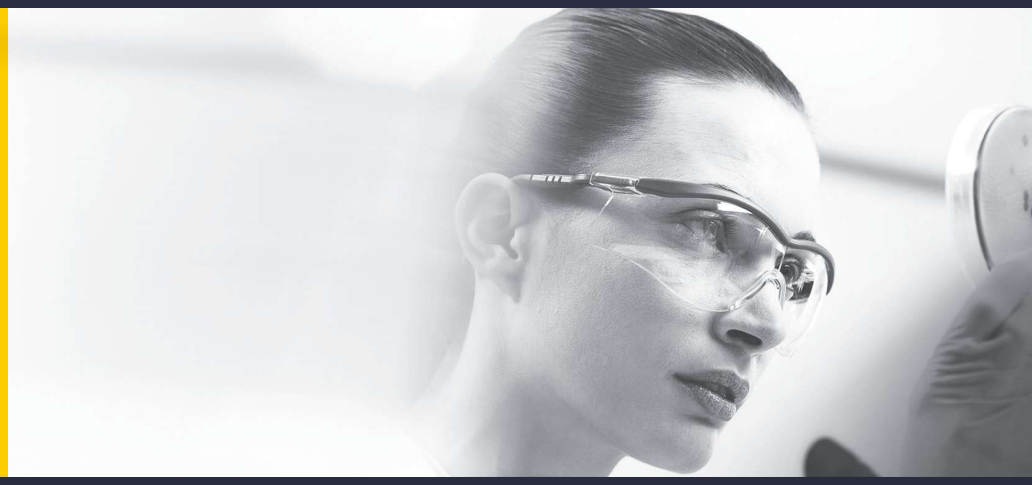

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