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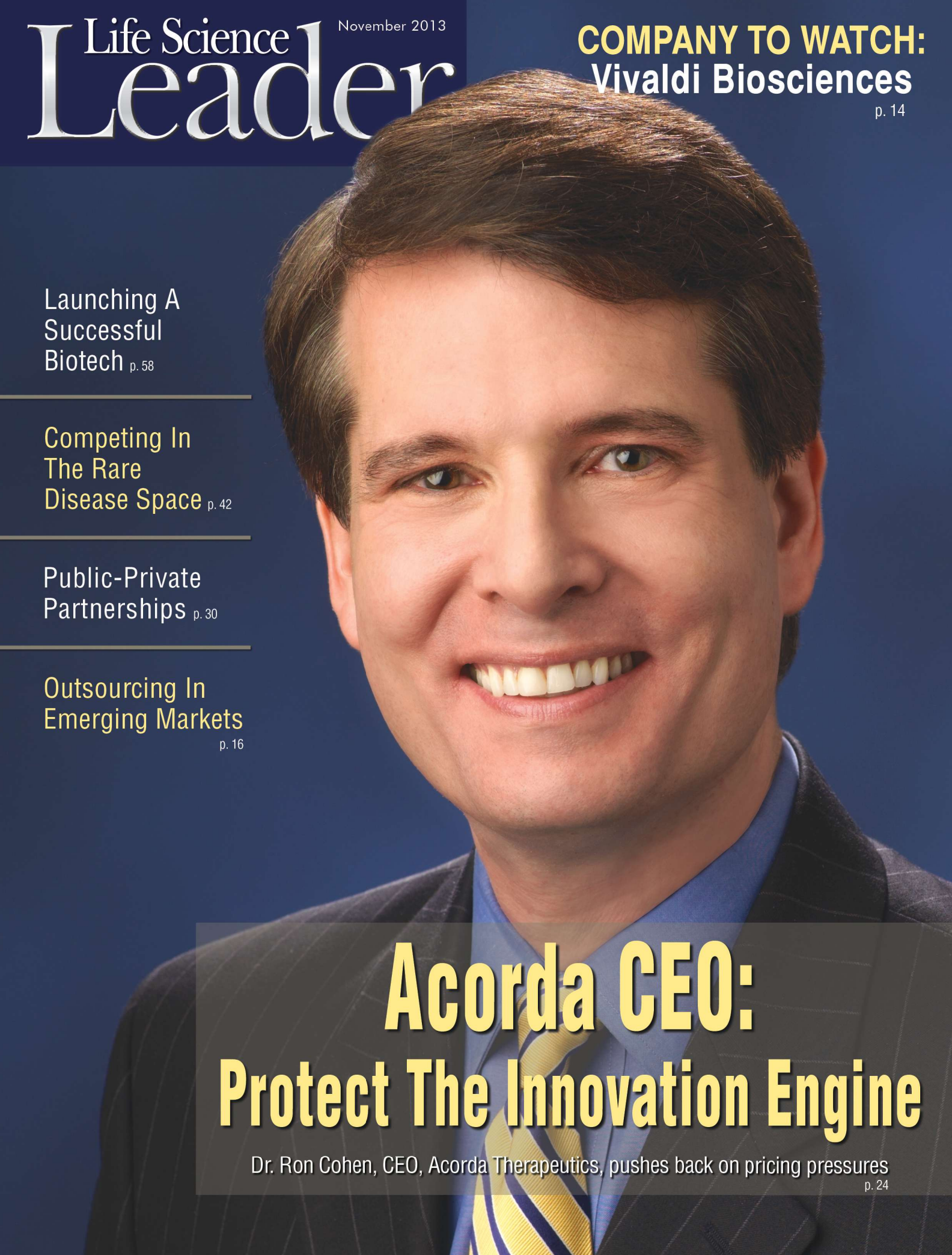

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Acorda CEO: Protect The Innovation Engine

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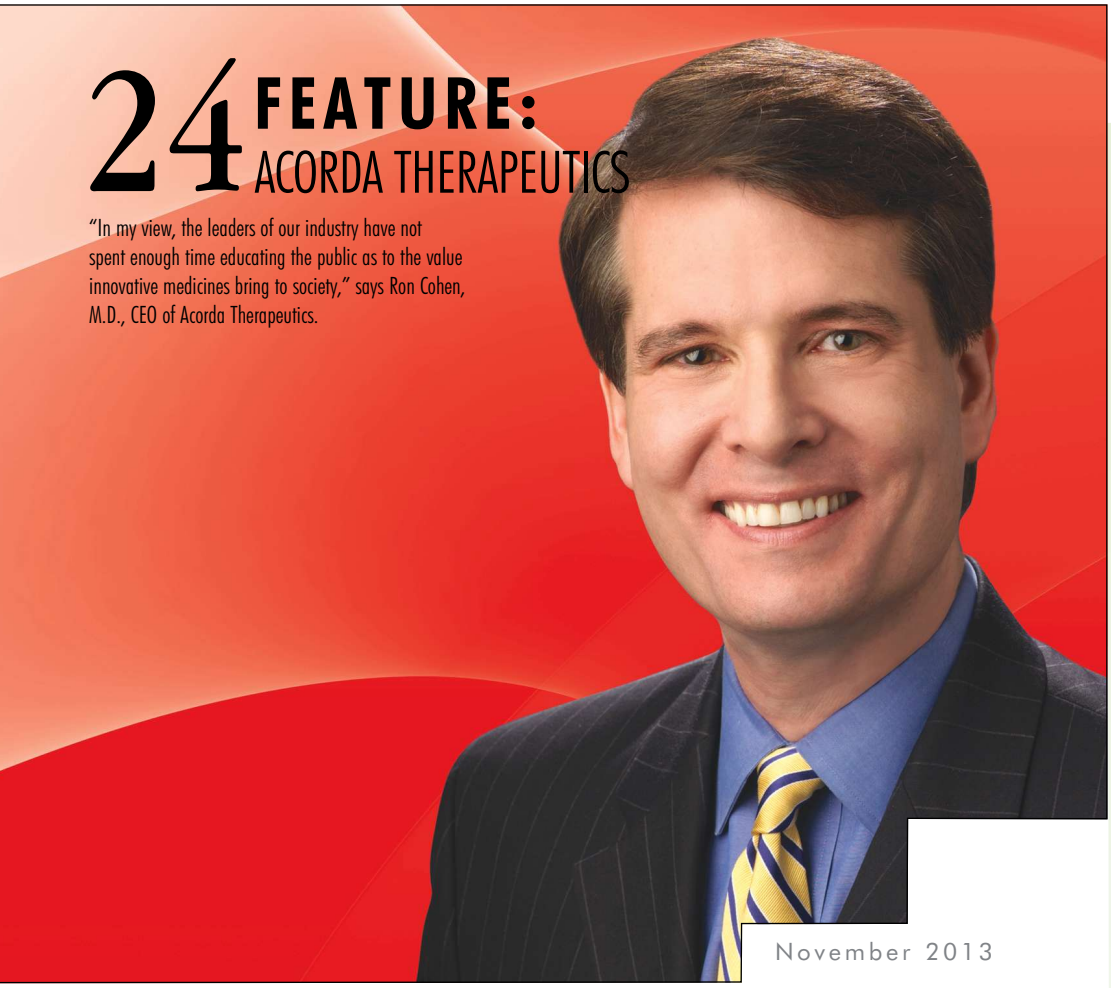
24 FEATURE: ACORDA THERAPEUTICS

"In my view, the leaders of our industry have not spent enough time educating the public as to the value innovative medicines bring to society," says Ron Cohen, M.D., CEO of Acorda Therapeutics.



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EDITOR'S NOTE

Lilly Lab Tour Reveals More Than Meets The Eye

In November 2012, I wrote the cover feature story, "Eli Lilly and Company — Open For Innovation." The article was based on an interview with Alan Palkowitz, VP of discovery chemistry, who shared insights on Lilly's (NYSE: LLY) Open Innovation Drug Discovery (OIDD) platform. While many companies have adopted the idea of open innovation, actions speak louder than words. Last month, Lilly Research Laboratories (LRL) opened its doors to a select group of media for a rare behind-the-scenes tour of three innovation labs (Alzheimer's disease, advanced analytics, and automated synthesis) at its global corporate headquarters in Indianapolis. My colleague Ed Miseta, chief editor for *Outsourced Pharma* and *Clinical Leader*, and I, along with representatives from *The Wall Street Journal, Scrip Intelligence, Indianapolis Business Journal, Indianapolis Star,* and *CBS* and *Fox TV* local affiliates, participated in a roundtable meeting with members of the LRL leadership team. During this discussion, we learned the focus of Lilly's Timely Valued Medicines (TVM) strategy, which has resulted in the company having one of the richest Phase 3 pipelines in its 135-year history. Of the 10 assets in Phase 3 clinical development, 9 were derived internally.

Not only did we get to hear from the leadership as to their various approaches to R&D, but we also got the opportunity to learn about the company's leader, Jan Lundberg, Ph.D., who joined Lilly in 2010 as EVP of science and technology and president of LRL.

Lundberg has authored more than 500 original articles in international peer-reviewed journals and is listed as one of the most highly cited authors by the Institute for Scientific Information (ISI). "If there is nothing to conquer, then life is boring," he explained. One of the current challenges Lilly is trying to conquer — finding a cure for Alzheimer's, a lengthy process requiring perseverance. In fact, a mantra of perseverance was evident throughout the tour.

Ronald DeMattos, Ph.D., led us through the Alzheimer's Disease Lab (*in vivo*), an ailment on which he has been focused for 15+ years. Steve Ruberg, who completed his Ph.D. in biostatistics, led the group through a tour of the Advanced Analytics Lab (*in silico*), demonstrating how Lilly is using computer modeling and simulation, predictive analytics, data mining, and analysis to improve clinical study design. Alex Godfrey, Ph.D., walked the group through the only fully integrated remote access chemistry lab in the world — the Automated Synthesis Lab (*in vitro*). While many have been critical of Lilly's failures, this tour revealed that people within Lilly are learning from these experiences and view successful drug discovery as a test of endurance to be persevered, not merely endured. (For additional insight into what Lilly is doing today, check out the interview with the company's global head of science and technology partnerships on page 30.)

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Q: What life sciences industry leader have you met who truly impressed you, and what could other leaders learn from this person?

Peter Green is now retired, after a 30-year career working for several leading pharma companies including GSK and Pfizer. I met him at Pfizer where he was a senior scientist with a Ph.D. in biochemistry. He was an exceptional leader who set clear expectations, followed through on priorities, and put his people first.

He said his proudest accomplishment was the many great people that he had the opportunity to help develop. I saw this firsthand at Pfizer. Those on Peter's team were engaged and motivated. Peter set high expectations, and he provided the support employees needed to do well.

Peter's advice to scientists entering management is timeless. "Don't be tempted to interfere with the scientists. You are now a manager; learn how to do this well, and enable the scientists to do their job well."

John Baldoni
John Baldoni is an internationally recognized leadership development consultant, executive coach, author, and speaker. John teaches men and women to achieve positive results by focusing on communication, influence, motivation, and supervision.

Q: What advice would you have for pharma/bio execs about preparing for a TV interview?

Focus on three to four key messages. Avoid industry-specific terms that a general audience might not know. TV interviews generally last only a few minutes, so make sure to logically work in your key messages during the first one to two questions. Rehearse working in your key messages regardless of the question. Memorize a few key statistics, anecdotes, or other details that support your positions. Tailor your messages to the audience. Watch a few interviews by the reporter you'll be working with to understand their style. If you get a random question, don't ignore it, but move quickly to bring the conversation back to your key messages.

Ron Cohen, M.D.
Cohen is president, CEO, and founder of Acorda Therapeutics, Inc., a public biotechnology company developing therapies for spinal cord injury, multiple sclerosis, and other nervous system disorders.

Q: What role should insurance companies play in the drug discovery process, and how best should this be facilitated?

Make no mistake about it, payers LOVE competition! Companies go into intense negotiations over pricing when they have to outbid another company for a major contract. Before starting any drug discovery program, you must have the end game in mind — i.e. will the insurance companies be willing to pay for it? How will the drug that emanates from this program effectively compete with existing or anticipated therapies when it is approved in 12 years? In areas where no therapy exists, this is a no-brainer. A new discovery approach fits this category. But let's say your idea is for a new approach to treat breast cancer. There are a number of compounds on the market to treat this disease and dozens more in development. How will your new approach, if successful, compare to what will be established therapy?

John LaMattina, Ph.D.
LaMattina is the former senior VP at Pfizer Inc. and the president of Pfizer Global Research and Development. In this role, he oversaw the drug discovery and development efforts of over 12,000 colleagues in the United States, Europe, and Asia.

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The Disastrous Launch Of Obamacare

President Obama's most ardent supporters now concede that the rollout of Obamacare has been disastrous. *Washington Post* commentator and Obamacare booster Ezra Klein stated that the launch of Obamacare "is not glitchy, not troubled, but a failure." He concluded that "The Obama administration's top job isn't beating the Republicans. It is running the government well. On this — the most important initiative they've launched — they've run the government badly."

Liberal comedian John Stewart grilled HHS Secretary Kathleen Sebelius and commented that it would take less time "to download every movie ever made than sign up for Obamacare." Indeed, two weeks into its launch, the healthcare consultancy Advisory Board found that just 5,000 people enrolled in Obamacare across the 36 states that rely on the troubled HealthCare.gov federal exchange website. The administration has refused to release its own data — it likely does not even want to know.

John McManus,
The McManus Group
jmcmanus@mcmanusgrp.com

Only a trickle of the 15 million individuals who visited the website in the first couple of weeks were able to actually enroll in a plan. Some individuals were able to register but never able to log in even after numerous attempts over a period of weeks. Others received a message to try later or just faced a blank screen. As a result, the number of visitors to the federal government's HealthCare.gov website plummeted 88 percent between Oct. 1 and Oct. 13, according to a new analysis of America's online use.

Just as troubling, for the few who have been able to enroll, plan premium and coverage information has been unreliable. Insurance companies report that some enrollment files were sent to the wrong insurer, and others have received inadequate income information from the government to determine the enrollee's subsidy and premium. Clearly, knowing whether individuals are enrolled in your plan and calculating their premium are rather fundamental components of making the program work.

WE SHOULD HAVE EXPECTED THESE PROBLEMS

Most frustrating of all, this still unfolding disaster was predictable. As I reported in my column a couple months ago, a June Government Accountability Office oversight report found that CMS was behind schedule in activities "that cross the core functional areas" in nearly every aspect of the exchange and was unlikely to be prepared by Oct. 1.

The administration repeatedly analogized the ACA (Affordable Care Act) implementation debacle to the initial glitches in the Medicare Part D drug benefit in 2006 that could be easily addressed and overcome. Jay Carney, spokesman for the White House, said, "There will be glitches in the rollout of this as there have been in every program. A good reference point is Medicare Part D, which caused a huge amount of consternation among consumers when it was initially rolled out."

But David Brailer, who worked as HHS' first national coordinator of health information technology during the launch of the Medicare drug benefit in 2006, pointed out that the administration should have anticipated that the federal exchange would trigger a rush of Americans onto the website, either as onlookers or outright buyers. In an interview with the *Washington Post* he noted the exchange was built to accommodate 50,000 to 60,000 visitors at a time — fewer than half as many as the enrollment site for Medicare drug benefit could handle, and at a time when use of the Internet is more ubiquitous.

When Medicare Part D was being designed, establishing a working software architecture was a priority, and the enrollment portal was online and being tested weeks in advance. The CMS plan finder worked for the vast majority of the millions of Medicare beneficiaries who selected a drug plan of their choice, enrolled, and now receive drug coverage with little incident.

Carney's analogy is unfounded and only furthers the administration's dismissive approach to addressing the fundamental shortcomings of the ACA statute and its implementation.

FINDING COMMON GROUND COULD HAVE HELPED

A sensible solution that could have gained bipartisan traction would have been to delay the rollout of the Obamacare exchanges for one year. But this would have required the Obama administration to acknowledge that it was unprepared to actually implement the law.

Of course, most Republicans had little incentive to

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assist with the rollout of a product they abhorred and campaigned against. But bipartisan consensus could have been forged to delay implementation of the exchanges and its subsidies because that would produce savings in the 10-year budget window, which could be devoted to other priorities, such as repealing the fatally flawed physician payment formula, minimizing certain incorrigible ACA provisions, or reducing the deficit as part of a debt-ceiling compromise (a proposal later proffered in the House of Representatives' second attempt to raise the debt ceiling). And more strident Republicans could have viewed a delay of Obamacare as an installment toward repeal.

But finding common ground between the parties on a controversial area like healthcare — and Obamacare in particular — actually requires dialogue between key policy makers. A conceivable conversation between key Republican and Democrat policy makers could sound like this: "You get a more orderly rollout of your signature achievement; we get a policy win on repealing an offensive aspect of that bill for which there is consensus — e.g. the medical device tax or the Independent Payment Advisory Board."

Republicans should not take unwarranted glee in the implementation challenges of Obamacare.

Real, substantive discussions between policy makers of the two major parties should be initiated by the executive office — people running the country.

For the administration to commence an uncomfortable and potentially embarrassing conversation of this nature, it must first examine the hard facts in a sober and analytical fashion. This requires the shelving of rote talking points designed to further political advantage and, instead, properly diagnosing a problem and starting to seek solutions.

Likewise, the Republican fixation on repealing Obamacare in the face of intractable odds has also deterred effective oversight of the program and a bipartisan dialogue on how to reform it. Instead of holding congressional hearings and focusing the public's attention on the unfolding implementation debacle of Obamacare, Republicans chose to tie Obamacare defunding to funding the rest of government operations precisely on the day that enrollment commenced — Oct. 1. It was a remarkably poor decision and terrible timing.

For all who can perform basic second-grade math, it was clear that Republicans needed not just 218 votes in the House and 51 votes in the Senate to defund Obamacare, but 290 votes in the House and 66 votes in the Senate. This two-thirds super-majority vote is what the Constitution requires to overcome a presidential veto. Even the most ardent opponents of Obamacare should acknowledge that President Obama was not going to sign a law repealing his signature achievement in which his name is now embedded. Senator Cruz's approach to defunding Obamacare was fundamentally flawed from its inception because there was no endgame.

Republicans should not take unwarranted glee in the implementation challenges of Obamacare, as it indicates a very strong public interest in signing up for the new coverage, and the open enrollment will last for six months. But they should refocus on proper oversight of the program and be open to reforming the program, which will certainly have huge implications on their constituents and the fiscal health of the country.

However, President Obama is the sole leader of the country. Flatly stating he will not negotiate, and refusing to acknowledge or comprehend the true disaster that is unfolding on his signature achievement, are no way to run the country.

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 draft 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. He can be reached at jmcmanus@mcmanusgrp.com.

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By Wayne Koberstein, executive editor

Vivaldi Biosciences

This early-research company seeks to fill current gaps in protection with a novel target and live-cell approach for development of superior seasonal as well as universal and pandemic flu vaccines.

SNAPSHOT

Vivaldi Biosciences is aiming to parlay its new vaccine target and live-cell approach to accomplish an unprecedented level of protection against the flu, using live attenuated influenza vaccines (LAIVs) to stimulate multiple arms of the immune system: antibodies, T-cells, and interferon. Its candidate LAIVs for seasonal and pandemic influenza have completed four randomized, double-blind, placebo-controlled clinical trials in a total of 245 volunteers. Vivaldi's LAIVs are based on manipulation of the influenza nonstructural protein (NS1) gene, with the goal of providing superior efficacy. NS1 is a virulence factor of the influenza virus.

Dr. Douglass Given
CEO
Vivaldi Biosciences

LATEST UPDATES

- October 2013: Acquired clinical-stage influenza vaccine assets from Baxter Healthcare SA.
- October 2013: Series B financing, first closing.
- Current: Entering a cooperative research and development agreement (CRADA) with the National Institute of Allergy and Infectious Diseases (NIAID) for pandemic influenza.

WHAT'S AT STAKE

When a CEO states an overwhelming record of failure in the area his company is working, you know the stakes are high. Speaking at the BIO Investor Forum in October, Dr. Douglass Given of Vivaldi cited 89 companies that had tried and failed to develop a universal flu vaccine, 55 of them in Phase 1 trials. Why should his company, alone, succeed? In so many words, it came down to two points: 1) Vivaldi's vaccines stimulate the immune system in new, multiple ways, and 2) unlike all the other candidates in the class, the company's vaccines are live.

"Live vaccines are considered the 'gold standard' for many other vaccine-preventable diseases — for example, polio and yellow fever — providing potent, long-lasting immunity with a low dose," says Given, in a post-BIF exchange. "Live vaccines also have excellent safety and efficacy records. The potential of a live vaccine for influenza has not been reached." He says FluMist, the only approved LAIV, is too attenuated to elicit a protective immune response in the elderly or for pandemic-flu protection.

Vivaldi's vaccines are also unique in targeting the NS1 gene, which affects virulence and is present in both A and B flu strains. "LAIVs with deleted or truncated NS1 generate a robust immune response — they stimulate the body's production of interferon, which acts as a natural adjuvant, activating the cellular immune response and enhancing production of antibodies, including neutralizing antibodies cross-reactive with variant (drifted) influenza strains," says Given. To the company's knowledge, it is a novel mode of action among all licensed influenza vaccines and vaccines in development.

"There is a tremendous need and very little innovation in the area of vaccines that provide superior efficacy in the prevention of seasonal influenza," Given maintains. "Most 'universal' vaccine approaches are years away from clinical evaluation."

Although the company wants a commercial pharma partner in the long run, it knows it must make a strong case for its approach with human data. "Many influenza vaccine development approaches fail because positive preclinical data do not translate to promising clinical results," Given says. "Vivaldi has strong preclinical and clinical data with its NS1 technology approach." Vivaldi already has data from a Phase 1 study of its LAIV against highly pathogenic avian influenza A(H5N1), or "bird flu," demonstrating proof-of-concept and tolerability.

Given says Vivaldi's approach will allow a rapid response to emerging strains through reverse genetics and plasmid rescue technologies, "reducing the time from strain isolation to start of vaccine manufacture." Vero cell-based manufacturing "addresses strategic needs in the event of an HPAI (highly pathogenic avian influenza) pandemic," producing LAIVs that are dose-sparing without the need for an adjuvant, and in nasal-spray form for mass use and self-administration in a pandemic setting. The company just strengthened its IP and technology options with the purchase of additional rights to NS1-based technologies, along with data from four related Phase 1 trials, from Baxter. If you want to watch any company forging ahead with the next generation of flu vaccines, you probably won't find one with a better case than Vivaldi.

VITAL STATISTICS

- Employees: 8
- Headquarters: Fort Collins, CO
- Finances/Funding: Vivaldi's investors, led by NGN Capital, have provided the company with $28 million. The company recently closed the first tranche of its Series B financing.

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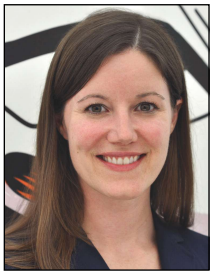

OUTSOURCING INSIGHTS

Outsourcing To CROs And CMOs In Emerging Markets In 2014

By Kate Hammeke, director of marketing intelligence, Nice Insight

In Nice Insight's most recent pharmaceutical and biotechnology outsourcing survey, 70 percent of all respondents indicated they would consider CROs and CMOs in emerging markets, such as Brazil, China, and India, when selecting suppliers for their upcoming projects. Of that 70 percent, 49 percent already work with an offshore supplier. Another 31 percent indicated they are aware of reliable businesses in emerging markets, but simply haven't worked with one yet. One in five said they are willing to outsource to emerging markets but do not know any reliable CROs/CMOs yet.

On the flip side, respondents who said they would not consider suppliers in emerging markets were primarily concerned about quality level (47 percent), followed by regulatory (33 percent) and intellectual property (26 percent). Complicated logistics and communication issues were each mentioned by 23 percent of respondents. Notably, 27 percent said they have simply not considered it.

There were some significant differences between buyer groups when it comes to offshoring to emerging markets. Big Pharma (71 percent), Biotech (70 percent), and Emerging Pharma (67 percent) showed a similar likelihood of considering offshore CROs and/or CMOs. However, Emerging Biotechs indicate they are much more likely to consider suppliers in emerging markets (86 percent), whereas Specialty Pharma sway strongly in the opposite direction, with only 61 percent considering this option. So it correlates that respondents indicating that their company considers emerging market suppliers are more likely to be involved in the development of biologics (81 percent) than those that don't (55 percent).

The volume of projects a company has to outsource may influence consideration of emerging market CROs/CMOs. Respondents who consider them reported that they will outsource an average of five different services in the next 12 to18 months, compared to an average of 3.3 services among those who don't consider emerging market suppliers. One could conclude that this might be influenced by cost, but that would be false. After all, the group that considers emerging market suppliers has a larger annual outsourcing expenditure, on average, than their counterparts who do not.

WHERE IS OFFSHORING HAPPENING THE MOST?

Ultimately, 1/3 of the survey respondents (34 percent) already work with suppliers in emerging markets. Those who do tend not to send all of their work offshore — they actually split their projects across several markets, with some inclusion of CROs and CMOs in emerging markets. Among these outsourcers, an average of 26 percent of projects will be awarded to businesses in the U.S. and Canada — a notable decrease from two years ago when this group reported that 36 percent of outsourced projects were awarded to North American businesses. This is a big trend worth noting. However, no single emerging market picked up a significant amount of the work shifted away from the U.S. and Canada — in fact, there was a 2 percent uptick in projects outsourced to China (17 percent), India (13 percent), Western Europe (12 percent), Argentina and Brazil (11 percent), and Eastern Europe (9 percent). The remaining 13 percent of outsourced projects was split among Korea, the Middle East, and Thailand and Vietnam.

It's likely that existing concerns about outsourcing to emerging markets will remain a barrier for some decision makers in the near future.

It's likely that existing concerns about outsourcing to emerging markets will remain a barrier for some decision makers in the near future. And there will always be projects that are best served by domestic suppliers for logistical or strategic reasons. However, data continues to indicate that there is a growing trend toward successful outsourcing to emerging markets, which is something all companies should consider in their long-term positioning strategies. We've heard reinforcement of this in qualitative interviews in the past year, and it also correlates with news reported this month relating to the implications of Obamacare.

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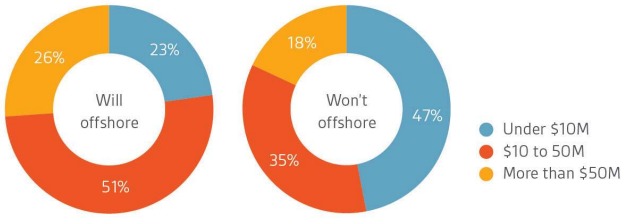
The Percentage of Respondents Who Would Consider Outsourcing to CROs/CMOs in Emerging Markets By Buyer Group

	Big Pharma	Specialty Pharma	Emerging Pharma	Biotech	Emerging Biotech	Overll
Will offshore	71%	61%	67%	70%	86%	70%
Won't offshore	29%	39%	33%	30%	14%	30%

The Average Number of Services to be Outsourced

5	3.3
Will offshore	Won't offshore

Outsourcing Expenditure



The Percentage of Outsourced Projects Assigned to Each Region By Buyer Group

	Big Pharma	Specialty Pharma	Emerging Pharma	Biotech	Emerging Biotech
Argentina & Brazil	10%	12%	11%	11%	14%
China	18%	16%	15%	17%	16%
Eastern Europe & Turkey	9%	10%	9%	9%	11%
India	17%	18%	14%	11%	13%
Korea	3%	3%	4%	5%	7%
Middle East	3%	2%	3%	3%	7%
Thailand & Vietnam	2%	2%	2%	3%	6%
US & Canada	24%	24%	34%	28%	17%
Western Europe	14%	14%	9%	12%	9%

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 composed 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.


Walker

If you want to learn more about the report or 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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BIO INNOVATION NOTES

Innovation In Stainless-Steel Bioprocessing

By Eric Langer (left), president and managing partner, and Ronald Rader, senior director, technical research, BioPlan Associates, Inc.

Anyone in the biopharmaceutical industry knows that one of the most active areas of innovation in biopharmaceutical manufacturing involves advances in single-use (disposable) technology. This involves bioprocessing equipment composed of plastics rather than traditional stainless steel. Single-use devices come presterilized, ready for use and disposal after single use. In contrast, bioprocessing classically has been done using fixed, stainless-steel equipment that requires in-house cleaning and sterilization prior to each reuse. Stainless-steel systems cost more than single-use and take longer to build. Although improvements in stainless-steel-based bioprocessing equipment have been less frequent, there will continue to be significant advances in stainless-steel-based bioprocessing.

During the past 10 years, the BioPlan annual survey of biopharmaceutical manufacturers has shown that biomanufacturers have been focused on single-use devices, and demand for new stainless-steel product innovations has lagged. Figure 1 below shows the differences in demand for innovation by end users for selected single-use devices compared with stainless steel. When asked in what areas (21 were listed) suppliers should concentrate their product development efforts, stainless-steel equipment ranked dead last at 4.9 percent.

STAINLESS IS HERE TO STAY

Despite this lack of industry interest in new and better stainless-steel systems, they are not likely to be replaced by single-use plastic systems. For example, single-use systems will probably never be as cost-effective at the largest manufacturing scales, such as for blockbuster antibody manufacture. Based on economics, most companies, including those using exclusively single-use devices for development, convert in later stages of development to stainless steel for cGMP commercial manufacturing.

The BioPlan annual survey also shows that stainless-steel facilities currently dominate larger-scale and commercial-product manufacture, while adoption of single-use systems remains negligible at larger scales. Currently, about 85 percent of those surveyed report manufacturing in stainless steel, and over 75 percent expressed a preference for stainless steel for new commercial manufacturing facilities. In contrast, single-use bioprocessing systems now dominate manufacturing at smaller scales, for R&D and early trials, with about two-thirds or more of new bioprocessing systems at these scales being single-use. The benefits (e.g. flexibility) that single-use provides have yet to surpass the overall economies of scale and lower manufacturing costs of stainless-steel systems used in larger commercial manufacturing. However, in comparison with upstream bioprocessing (e.g. bioreactors), downstream bioprocessing innovations (e.g. chromatography) have been fewer and less significant, with much less adoption of single-use equipment.

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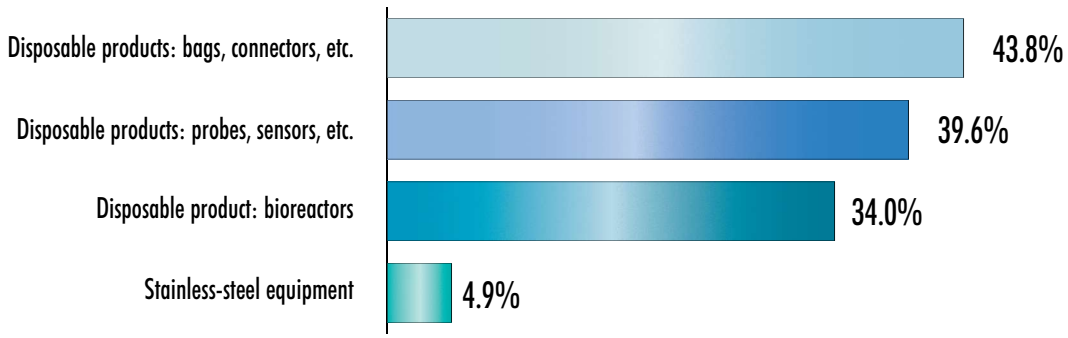
Figure 1: Selected New Product Development Areas Of Interest

Top Areas Suppliers Must Focus Development Efforts On



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more cost-effective versus single-use for commercial product manufacture (where productivity is most important, and flexibility and related changes are less significant). Despite rapid adoption of single-use systems at smaller scales, use of stainless steel is and will continue to grow, just not as rapidly. Even 10 years from now, and perhaps longer, stainless steel will remain the dominant commercial bioprocessing platform, with single-use adoption for commercial manufacture continuing to ramp up.

In fact, most of the largest facilities — built in the 1980s and 1990s and commonly described with terms such as "legacy" or "dinosaurs" — are still in use and overwhelmingly provide most of the world's biopharmaceutical manufacturing capacity.

Stainless-steel bioprocessing equipment, especially for commercial-scale manufacture, has changed little in recent decades. And until recently, most of the innovation has come from the processing performed in the stainless equipment. But stainless equipment manufacturers continue to innovate, and indications are that there will be increasing incremental improvements. For example, according to Andrew Powell, VP and GM at CRANE CPE, innovation in stainless steel bioprocessing is a primary focus. "At Saunders, we recently released our Stainless Steel S360 actuator range, and we're investing heavily in new product innovation. In the near future, I would expect to see even more substantial improvements in processes using stainless equipment."

These improvements are needed, as most of the largest stainless-steel facilities are operating below capacity. Some are being converted to more adaptable multiuse facilities. In many cases, this involves radical innovation in business practices, with many of the largest and most established manufacturers now offering CMO services (e.g. GlaxoSmithKline) or concluding manufacturing agreements with other companies (e.g. MedImmune/AstraZeneca manufacturing for Merck & Co). Thus, innovations continue to drive expanded use of stainless steel.

MAJOR TECHNOLOGICAL TRENDS DRIVING INNOVATIONS IN STAINLESS-STEEL BIOPROCESSING:

Higher titers: Better cell lines and expression systems continue to increase yield, making it possible to specify stainless-steel equipment at smaller scale.

Sensors: There are not only few but sometimes inadequate sensors for most relevant analytes for single-use applications. Those available are primarily for use with stainless-steel systems. So, stainless-steel systems have clear advantages in terms of providing process data.

Automation/process control: Most stainless-steel facilities now have state-of-the-art, real-time process monitoring and control systems. These systems, combined with more and better sensors, PAT (process analytical technology), and other efforts to make optimal use of process data, enable better control and documentation of bioprocessing.

Perfusion: Perfusion (i.e. involving retaining higher levels of cells and expressed products in bioreactors using filter pumps) or other methods such as centrifugation enable the use of even smaller bioreactors. Perfusion devices are increasingly being adopted and added to many stainless-steel facilities.

Hybrid systems: Many stainless-steel facilities are slowly adapting single-use equipment into their existing facilities. This involves single-use equipment where it provides significant or needed advantages over stainless steel, for example, single-use membrane filters. This will require specialized compatibility innovations.

Business models: As yields go up, many companies with large, in-place stainless-steel facilities and unused capacity are offering manufacturing services to other companies. This is a radical change for some companies. Relatively few stainless-steel facilities have yet to be mothballed or dismantled, with most still in use.

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 methodology 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.

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

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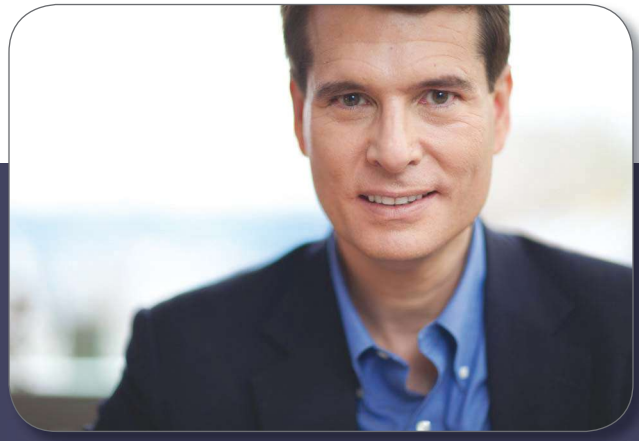
Ron Cohen, M.D., CEO, Acorda Therapeutics

From Obscurity To Innovation Engine — The Evolution Of Specialty Pharma

BY ROB WRIGHT

Twenty years ago when I first started in the life sciences industry, specialty products for rare diseases had the feel of being a company's charitable contribution to society. I recall sitting in a new-hire training orientation listening to the instructor inform us how the profits from our cash-cow products supported the R&D and distribution of the specialty products designed to help the unfortunate few suffering from rare diseases. How times have changed! Today, specialty drugs represent the fastest-growing sector of pharmacy spending. A recent Express Scripts Drug Trend Report has specialty drugs at an annual cost of more than $290 per member per year (PMPY) in 2012, up from $170 PMPY the year prior. By 2018, it is estimated specialty drug spend will surpass traditional drug spend and PMPY will reach $845. In just three



"ORPHAN-TYPE DRUGS ARE OFTEN BIOLOGICS WHICH TEND TO BE VERY COMPLICATED TO PRODUCE."

Ron Cohen, M.D., CEO, Acorda Therapeutics

years, market research intelligence firm EvaluatePharma projects 7 of the top 10 bestselling drugs (by revenue) will be specialty drugs and the category accounting for nearly half of all pharmaceutical manufacturer sales. Some have described the category's growth as staggering and question how insurance companies will be able to afford paying for what often proves to be lifesaving treatments for patients suffering from rare diseases.

Ron Cohen, M.D., would like to remind people who are concerned about insurance companies being able to afford paying for medicines of one simple fact: Prescription drugs account for about 10 to 12 percent of the total U.S. healthcare spend. "We are one of the great innovative engines providing society with desperately needed goods which are more valued than the latest iPad or video camera," he attests. Cohen founded Acorda Therapeutics (NASDAQ: ACOR), a specialty pharmaceutical company, back in 1995. The physician-turned-CEO shares insights on the evolution of the U.S. specialty pharmaceutical industry from obscurity to significance. In addition, he explains the current insurance conundrum and his concern around its having the potential to stifle pharmaceutical industry innovation. Finally, Cohen places a call to action for industry leaders to educate U.S. stakeholders (i.e. consumers, patients, families, media, and elected officials) on the value proposition specialty drugs offer as drivers of innovation.

FROM OBSCURITY TO SIGNIFICANCE — THE EVOLUTION OF SPECIALTY PHARMA

For the 10 years prior to the passage of the Orphan Drug Act (ODA) of 1983, the pharmaceutical industry averaged less than one specialty pharmaceutical product per year. In the 30 years since, the FDA Office of Orphan Products Development (OOPD) notes industry having developed and marketed more than 400 rare disease drugs (a little over 13 per year). Under the ODA, drugs, vaccines, and diagnostics agents would qualify for orphan status if they were intended to treat a disease affecting fewer than 200,000 American citizens. "Unlike the usual chemistry-based pills," Cohen notes, "Orphan-type drugs are often biologics which tend to be very complicated to produce." In addition, these drugs are for relatively small populations and manufactured in fairly low volumes. The result is products that are very risky to develop, costly to produce, and thus, very expensive when they make it to market. For example, in January, Sanofi's Kynamro (mipomersen sodium) injection received approval for treatment in patients with homozygous familial hypercholesterolemia (HoFH) — a disease occurring in approximately 1 in 1 million people. The annual cost for Kynamro is about $176,000 a year. It will be competing with Aegerion Pharmaceuticals' Juxtapid (lomitapide) capsules which cost $235,000 to $295,000 a year. In the U.S. these two drugs have a viable market of about 300 patients annually. To encourage companies to develop specialty pharma drugs for such small markets, the ODA included a number of incentives including tax credits, drug development grants, fast-track FDA approval, and a seven-year market exclusivity period. This was different from traditional patent protection, as the period of exclusivity did not begin until the drug was granted FDA approval.

THE INSURANCE CONUNDRUM

Though there is some debate as to whether the ODA really stimulated the production of rare disease drugs, the increased output of the past 30 years cannot be denied, having resulted in $80 billion in sales a year in the U.S. alone. As specialty pharmaceuticals gained in popularity, so too did issues surrounding the process of managing their costs. The passage of the Medicare Modernization Act in 2003 and the subsequent implementation of the Medicare Part D program included a specialty tier in order to help define what qualified as a specialty drug. "Those specialty tiers are entirely cost-based, so it's irrespective of whether it's a biologic or chemistry-based or oral or injectable," Cohen states. "Basically, if it costs more than $600 a month, it gets specialty status." Other characteristics include:

- complex treatment regimens requiring ongoing clinical monitoring and patient education
- special shipping, storage, or delivery requirements. generally biologically derived, available in injectable, infusible, and oral forms
- dispensed to treat individuals with chronic or rare

diseases often having limited or exclusive product availability and distribution
- treat therapeutic categories such as oncology, autoimmune/immune, and inflammatory that are marked by long-term or severe symptoms, side effects, or increased fatality.

"Complex biological drugs require more sophisticated handling," Cohen explains. Complicated dosing regimens such as systemic application by infusion or injection or requiring physician supervision for administration are what Cohen describes as being high-touch interactions, which further add to the cost of these drugs. To address the high-touch needs of these patients, specialty pharmacies grew from a cottage industry to big business. "Specialty pharmacies realized they could provide an advantage over traditional retail for these patients," Cohen attests. In addition to providing better service than traditional retail pharmacies to these high-touch patients, specialty pharmacies and pharmacy benefit management (PBM) organizations gained popularity as a means of reducing drug costs. It is estimated that more than 200 million Americans receive drug benefits administered by PBMs, which are able to aggregate the buying clout of millions of enrollees and thereby lower prices through discounts, manufacturer rebates, and improved distribution efficiencies. "If you look at the evolving landscape, the boundaries have been totally blurred, because commercial payers own specialty pharmacies and PBMs that manage the pharmacy benefits for the reimbursement of companies," Cohen states. This blurring of boundaries results in a potential conflict of interest. "A specialty pharmacy owned by a large insurance company or payer wants to get contracts for manufacturers to distribute their drugs because that's how they get paid," he explains. "The reimbursement side may want to limit access to those specialty drugs because they cost a lot."

According to Cohen, when it comes to reimbursing for specialty pharmaceuticals, "It benefits the payers to scrutinize and exert control." There are a number of ways insurance companies do this, such as specialty-tier structuring with significantly higher co-pays, prior-authorizations, and step edits. "It is just a thicket of regulations and requirements," states Cohen. "In some cases, the standards imposed by insurance companies don't make medical sense to practitioners because they are done in a highly variable way." This unwillingness of the system to pay for a drug is one of Cohen's biggest concerns.

THE EU'S SHORTSIGHTED COST-CONTAINMENT POLICIES

"The burden for paying for a pharmaceutical innovation is falling quite disproportionately on the United States' system," Cohen says. This is because of the pricing power available in the U.S. Cohen believes the extent to which insurance payers don't pay for specialty drugs has the potential to stifle U.S. pharmaceutical innovation. Take the EU as an example.

"Europe, which has a government pay system, has taken the approach of squeezing pharmaceutical industry margins," he explains. "What you're finding is some of the bigger, multinational companies are now moving operations out of Europe. In some cases, these companies have decided not to distribute certain new drugs in Europe, because the price does not reflect the innovation or benefit of the drug nor the investment of the company to bring it to market." On a small scale, take Acorda's Ampyra (dalfampridine) extended release 10mg tablets, approved by the FDA for people with multiple sclerosis (MS) and marketed as Fampyra outside the U.S. through a license and collaboration agreement with Biogen Idec (NADAQ: BIIB). Acorda projects the drug will do between $285 and $315 million net sales this year. "Of that, we are going to spend $60 to $70 million in R&D," he explains. "That's a pretty high percentage of our net sales." The

CHIPPING AWAY AT PHARMA'S ABILITY TO INNOVATE

One of Ron Cohen's biggest fears is that people in power and government who use the biopharmaceutical industry as a whipping post will continue to layer on more regulations to extract more discounts and payments from the pharma industry. "For example, the industry agreed to cover initially 50 percent of the 'donut hole' of Medicare and then increasing percentages over the ensuing years," explains Cohen, CEO of Acorda Therapeutics. "This is tens of billions of dollars of payments and discounts." According to Cohen, the industry did this with the understanding that the Affordable Care Act (ACA) would enable more people to have access to insurance coverage. "In effect, we're giving a substantial discount on the medicines, but we're getting more customers," he explains.

This all changed with the June 28, 2012, Supreme Court decision ruling that the federal government could not force the states to accept the Medicaid expansion. "Now, it's unclear how many Medicaid patients are really going to come in under the expansion, because already 25 states or so have said they are not going to participate," Cohen says. "And they are pushing to extract still more discounts from the industry for Medicare dual-eligibles, subjecting them to the same 23 percent plus discounts Medicaid gets." Cohen describes these decisions as a continual chipping away at the financial health of the industry, and thereby, at its ability to innovate and provide society with the new medicines it needs.

reason Acorda can invest nearly 22% of sales into R&D is because the company gets a reasonable rate of reimbursement for the drug in the U.S. In the EU, however, reimbursement is significantly less. Cohen believes the pharmaceutical pricing and reimbursement policies (e.g. external reference pricing [ERP]) outlined in the September 2012, European Commission Economic Papers 461 – *Cost-Containment Policies in Public Pharmaceutical Spending in the EU*, "will prove to have been shortsighted and extreme and not constructive for supporting innovation in drug development. If this were to happen in the U.S., there would be, in effect, nothing paying for pharmaceutical research and innovation." Cohen believes a European style of reimbursement in the U.S. could open up opportunities for countries like China to take the lead.

A state-run system, China developed a five-year plan allocating billions of dollars specifically earmarked to advance certain industries, including biopharmaceuticals. "We don't have the luxury of a government entity pouring money into our industry," he attests. "We have to earn it through the value of the products we produce. If we're not getting reimbursed at the current level, then R&D and innovation are clearly going to suffer. I don't think this is really arguable." Cohen asks, "How are we willing to pay for our future medical wellbeing?" This is a message he feels pharmaceutical and biotech companies need to communicate better.

According to Cohen, it is incumbent on specialty pharma to clearly communicate the value of a medicine, even those considered very expensive.

WHAT IS THE VALUE OF A MEDICINE?

Cohen believes that the pharmaceutical industry has been a convenient target for public angst for too long. "If you read the papers and watch the news, you would likely think prescription drugs make up 75 percent of all healthcare costs," he states. Consider this recent headline in the *Wall Street Journal* — "Drug Makers See Profit Potential In Rare Diseases." Cohen attributes this misperception to the pharmaceutical industry's profitability and rare commentary on other drivers of rising healthcare costs. A recent article published in the *American Journal of Managed Care* (March 2013) showed hospitals, not pharmaceuticals, as being the primary driver behind spiraling healthcare costs. Accounting for more than 30 percent of all U.S. healthcare expenditures, the average cost per hospital stay in the U.S. ($15,734) is three times the cost of the next closest country, Germany ($5,004). In addition, data showed provider consolidation through hospital mergers or the buying up of physician practices resulted in "higher prices for services, higher costs for patients, and often no improvement in the quality of care delivered." According to Cohen, it is incumbent on specialty pharma to clearly communicate the value of a medicine, even those considered very expensive. "Yes, a company might charge $50,000 a year for a drug, but if you look at the outcomes for the patients and see that it prevents hospitalizations which cost $100,000, then you would gladly pay for this drug," he affirms. "In other cases, drugs may improve lives without necessarily showing as direct a line toward decreased costs, for example, drugs that improve walking ability or that reduce pain, yet still are highly important to patients. It is dangerous to try to assert, as for example Europe increasingly is doing, that drugs are only valuable if they can be proved to reduce overall costs. This ignores the intrinsic value in improving the lives of people suffering with disease and disability."

A little over a year ago, Vertex Pharmaceuticals (NASDAQ: VRTX) gained FDA approval for the first drug that treats the root cause of CF (cystic fibrosis), Kalydeco (ivacaftor). At a cost of $294,000 for a year's supply, it is one of the most expensive drugs in the U.S. Cohen notes however, that the research conducted by Vertex is leading to other discoveries and providing opportunities to treat even more patients with differing strains of CF — a point often overlooked when one focuses only on cost. "In my view, the leaders of our industry have not spent enough time educating the public as to the value innovative medicines bring to society," Cohen states. "There needs to be a much greater effort on the part of industry to educate patient groups, since those patient groups have the power to advocate for open access to medicines." Cohen believes the pharma industry is part of a solution, not part of the problem. He advocates for the industry to stop taking such a defensive stance and begin offering some positive offense. To support educating and gaining industry advocates, Cohen supports the industry utilizing existing coalitions such as PhRMA and BIO to develop public service announcements designed to reach a wide audience. "If everyone would contribute to ongoing public service ads about what we do, the number of drugs produced, and the number of lives improved or saved for the various conditions, instead of just advertising the latest erectile dysfunction drug, we could change the perception of our industry from convenient whipping post to innovation engine and creator of life-enhancing medicines."

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How To Take Charge Of Your Public-Private Partnerships

BY ROB WRIGHT

The process of creating a public-private partnership (P3) can be very challenging. First, consider the size of the organizations involved. The NIH, the largest source of funding for medical research in the world, consists of 27 institutes and centers alone. The University of Texas M.D. Anderson Cancer Center has over 1,100 clinical resident fellows. Even for a company the size of Eli Lilly and Company (NYSE: LLY), the navigation of academic and government-institution policies and procedures for brokering a partnership can be a labyrinth.


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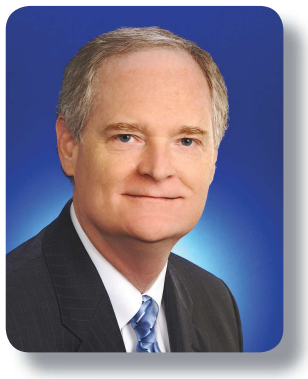
> **"THERE ARE FAR MORE CRITICAL UNANSWERED QUESTIONS THAN THERE IS MANPOWER AT LILLY TO PURSUE."**
>
> Dale Edgar, Ph.D., global head of science and technology partnerships, Lilly



Additionally, outcomes are often not in alignment. For example, folks at Lilly are charged with developing innovative medicines that are both safe and effective for patients while providing a return to its shareholders. The typical academic researcher is striving to create cutting-edge scientific discoveries that can be published in a high-profile peer-reviewed journal.

If you are a pharmaceutical company wanting to leverage the full potential of P3s, where is the best place to start? Lilly has embraced a multipronged approach toward developing and implementing its P3 strategy. First, Lilly created an executive-level position responsible for the global strategy and governance of P3s. Second, the company placed an individual in the position with experience in traversing the P3 maze. Third, Lilly launched a postdoctoral fellowship award program. Finally, the company developed its P3 objectives and identified opportunities to advance its work in this area.

In August 2012, as part of the company's larger external innovation strategy, Dale Edgar, Ph.D., took on the responsibility for consortia and P3s across Lilly's research enterprise in the newly created position of global head of science and technology partnerships. A former associate professor at the Stanford University School of Medicine, he has had his share of NIH and DoD grants and industry-sponsored projects that delivered a strong list of publications. He ultimately spun out his laboratory at Stanford to found a start-up biotech company called Hypnion Inc., which Lilly acquired in 2007. The translation of Edgar's basic research, from the bench to the bedside, resulted in numerous patents. Here, Edgar shares his insights on Lilly's strategy and governance approach to P3s, starting with the creation of the company's global postdoctoral scientist training program.

PEER-TO-PEER SCIENTIFIC APPROACH TO PARTNERSHIPS

"When we create a partnership," Edgar explains, "we don't pitch money over the walls and then wait for results." This is what Edgar defines as a traditional sponsored project. "A real partnership is where you're working together in real time, hand in hand." For example, at Lilly, this involves a peer-to-peer relationship between Lilly scientists and academic and government researchers. To do this, Edgar believes you first need to create a trust-based peer-to-peer culture within your organization. So in addition to placing Edgar, a former academic peer, in charge of brokering academic relationships, Lilly seeks ways for its scientists to engage with external researchers in a peer-to-peer capacity. "To help build relationships, trust, and the common sense of purpose that is vital to innovation, we created the Lilly Innovation Fellowship Award (LIFA)," Edgar explains. This competitive postdoctoral fellowship provides up to four years of funding for exceptional postdocs, so they don't have to constantly be looking over their shoulder for money and, instead, can spend all of their time innovating. This includes a full salary and benefits paid by Lilly, as well as a $5,000 annual stipend for travel expenses. Here is how it works.

The LIFA program is both an award and a partnership-based training program, with a Lilly mentor, an academic mentor, and a postdoc, all creating what Edgar refers to as an innovation triad. What Edgar likes about this approach is that both the academic and industry mentor are working together in the interest of the postdoc's success (the common sense of purpose). This not only creates a high-trust peer-to-peer relationship between the parties, but also establishes connectivity and a mutually beneficial flow of innovation through the postdoc. "Lilly receives nominations from our scientists as to which universities and institutions they believe can help us address five grand challenges that are broadly relevant to the pharmaceutical industry." Those challenges are:

- to establish clinical efficacy and safety earlier in the drug development process
- to develop the right medicine for the right patient
- to deliver exceptional patient outcomes
- to simplify large-scale chemistry and protein production and minimize its environmental impact
- to target and deliver biologics and small molecule drugs precisely and safely.

"P3s are an especially powerful strategy for answering a wide variety of critical unanswered questions embodied by the grand challenges," he states. A small sample of potential critical unanswered questions include:

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- What is the best way to objectively segment patients with disease to understand why some are responders to medication and some are not?
- Controlling for diet and environment, why are some individuals at greater risk for Type 2 diabetes?
- Can in silico informatics technologies predict behavioral pharmacology?
- Can large-molecule medicines be made orally available and brain-penetrant?
- Who are the caregivers of the 21st century, and what are the disease/health risks of their occupation?

Lilly solicits LIFA applications by invitation only through the deans of nominated schools and institutions. Lilly senior scientists then review the applications for innovative merit with emphasis on innovative concept and the qualities of the postdoc and academic mentor. Finalists were selected in April of this year and invited to Lilly for interviews. From June to October, Lilly performs the onboarding process for LIFA recipients. The postdoc will spend a certain amount of time working at both the academic institution and Lilly, depending on the nature of the project. Postdocs and their academic mentors will typically be located in the same continent as the relevant Lilly research laboratory, which can include sites in the U.S., U.K., Spain, Singapore, and China. Edgar believes working at Lilly is part of the incentive to participate in the program since it provides the postdoc with access to Lilly resources and technologies not typically available in academia. The company also provides funds to the academic institution in support of the training partnership. "Maybe they decide they need to buy a new tool, supplies, or send the postdoc to a meeting. It's completely up to them what they do, as long as the money is used to support the postdoc," says Edgar. The annual payment to an institution in the United States is $45,000. The program also benefits the academic mentoring investigator, because they will be a principal author on the resulting publications, as the research is largely precompetitive in nature.

"There are far more critical unanswered questions than there is manpower at Lilly to pursue. Indeed, we certainly do not have all the answers we need to deliver innovative medicines to patients who are waiting." Edgar believes that incorporating P3 as part of the long-term research strategy and engaging postdoctoral scientists and other relationship-based frameworks are vital to the transformation of the pharmaceutical industry. "This is how we bring great minds together to help solve the biomedical challenges of our time," he asserts.

COLLABORATING WITH ACADEMIA

Academia and industry are aligned in their desire to deliver innovative medicines to patients and see this as more than useful symbiosis. P3s enable academia and industry to join forces in a noble cause. But differences between academic and industry cultures present challenges. Publication is the currency by which academic scientists are judged for future NIH funding, promotions, tenure, and the most precious of all currency in academic institutions — the size of an academic investigator's laboratory space. Yet protecting IP is critical to industry, and publishing research too soon can threaten a company's IP. For this reason, the vast majority of P3s are precompetitive in nature — fundamental science, tools, and techniques that can be readily published. There is an unrelenting appetite for precompetitive P3s, especially with limited NIH and other federal research funding. More universities throughout the United States are building drug discovery centers with the goal of producing valuable new medicines for patients in partnership with industry.

> **"IN EUROPE, WE WORK WITH THE INNOVATIVE MEDICINES INITIATIVE (IMI)."**
>
> Dale Edgar, Ph.D., Lilly

SEEK ENGAGEMENT FOR PUBLIC-PRIVATE PARTNERSHIP SUCCESS

When Lilly seeks to engage with the global medical innovation ecosystem, Edgar says it is driven by first thinking of the critical unanswered questions he previously described. "We present those critical unanswered questions into different mechanisms or forums," he states. There are a number of ways in which Lilly does this. "In Europe, we work with the Innovative Medicines Initiative (IMI)," he explains. IMI is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. Members of the IMI governing board include representatives from industry (e.g. Lundbeck, Genzyme, Novartis, UCB), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the European Commission. Lilly presently has 19 projects with IMI, all seeking to address at least one critical unanswered question. "All the projects are precompetitive," he states. "However, all are driving to solve something that we know will help us in our programs to speed up the breakthroughs."

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The company has similar initiatives in the United States. For example, Lilly is actively engaged with the NIH's National Center for Advancing Translational Science (NCATS). Edgar explains, "NCATS has created the Clinical and Translational Science Awards, CTSA program." The CTSAs provide support, infrastructure, and resources for clinical research around the country, providing academic homes for translational sciences, which is similar to Lilly's LIFA initiative. The NCATS program is also creating Centers for Clinical and Translational Science (CCTS) throughout the United States, in partnership with academic institutions (e.g. Spectrum: The Stanford Center for Clinical and Translational Education and Research). "The CCTSs have also self-assembled into regional consortia that we have been engaging via the critical unanswered question approach," he states.

Under the NCATS program, there is a mandate for academic industry partnerships to help facilitate the translation of research for the benefit of patients. For example, according to Edgar, 20 years ago, the vast majority of molecules in development would fail for toxicology. Through a number of concerted efforts within industry, different technologies were created that helped reduce the risk of compounds failing for technical reasons. For example, early discovery efforts now include in situ salt screening, preclinical toxicology, *in vitro* genetic toxicology and metabolism studies, quantitative pharmacology, and other steps to increase development success of candidate molecules. "Nowadays, less than 10 percent of molecules die for toxicology reasons in Phase 2 clinical trials, while considerably more fail for efficacy reasons," he says. "The NCATS program was created to help reduce clinical trial failures due to insufficient efficacy by developing predictive biomarkers and fostering studies to better understand how medicines can be targeted to those patients most likely to benefit. If you help reduce Phase 2 and Phase 3 failures, you can potentially shave years off the drug development process."

PARTICIPATING IN THE TRANSCELERATE BIOPHARMA PROGRAM

Another program Lilly is actively involved with is TransCelerate BioPharma, which is also designed to develop and share industry research and solutions to simplify and accelerate drug discovery and development. The initiative was started by 10 biopharmaceutical companies, including Lilly, just one year ago, and has already managed to develop common clinical-trial site qualifications and create a standardized methodology for risk-based monitoring of clinical trials. It also recently established the Clinical Trials Comparator Network to establish reliable and rapid sourcing of quality drug products for use in clinical trials via a master service agreement between TransCelerate members. "It's a very action-oriented consortium," Edgar states. "Everything in TransCelerate is about improving the quality and speed of the drug development process." According to Edgar, the TransCelerate initiative will also help the FDA. For example, by companies collaborating and developing standardized modules within a regulatory submission package, the agency will become familiar with the format. "When industry understands what the FDA needs, it is easier to deliver the information required in a standardized way, making it easier to be processed," he states.

Edgar describes P3 engagement as an active process of seeking out the academic pillars of excellence. For example, in 2008, Lilly created a public-private partnership called the Center for Cognitive Neurosciences (CCN). This was a partnership between Lilly and six academic centers in England. "Before this program, not only did these six academic centers not interact with each other, they overtly competed with one another," he states. "We brought them together by focusing on trying to solve tough questions in the area of cognition, which would ultimately help patients with Alzheimer's disease, neuropsychiatric disorders, and Parkinson's disease."

"MY ADVICE TO ANYONE LOOKING TO BECOME INVOLVED WITH PUBLIC-PRIVATE PARTNERSHIPS IS TO DETERMINE YOUR OBJECTIVES, DEVELOP AND FOSTER RELATIONSHIPS WITH ACADEMIA IN YOUR LOCAL AREA, AND REACH OUT TO THE NIH."

Dale Edgar, Ph.D., Lilly

By placing a former academic researcher in a position to head up the brokering of peer-to-peer relationships, along with the creation of a postdoctoral science training program, Lilly is well positioned to capitalize on the open-innovation industry trend. "That framework has done a lot to help align academia and industry toward the common goal of really trying to find ways to build science and create a sense of urgency around that science — to take us through the right steps to deliver innovation to patients," Edgar says.

As a result of this work, today Lilly is engaged in more than 50 consortia and P3s. "My advice to anyone looking to become involved with public-private partnerships is to determine your objectives, develop and foster relationships with academia in your local area, and reach out to the NIH," says Edgar. "Today's health challenges are vast and complex. There is opportunity for us to all collaborate as a way to help accelerate the delivery of innovative medicines to patients."

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Robin Smith, M.D.,
chairman and CEO, NeoStem

NeoStem's CEO Spearheads Nontypical Collaboration

By Rob Wright

There are three taboo topics at work — sex, politics, and religion. You would think discussing science should therefore be acceptable. However, strike up a conversation on stem cell research, and you're likely going to be covering all three of those taboo topics.

Now imagine you are the CEO of a stem cell therapy research and development company, and you decide to discuss the benefits of stem cell research with the executive leadership of one of the largest and wealthiest organizations in the world, which, by the way, has also taken a firm and very public position against the use of embryonic stem cell research — the Roman Catholic Church. That is exactly what Robin Smith, M.D., chairman and CEO of NeoStem (NASDAQ: NBS), decided to do. Not only did Smith strike up a conversation, she and the team at NeoStem successfully orchestrated what has been characterized as the Vatican's first-ever contract of collaboration with an outside commercial venture to advance adult stem cell research.

This unprecedented initiative pairs NeoStem and the Stem for Life Foundation (SFLF), a public charity it helped form and for which Smith serves as president and chairman, together with the Pontifical Council for Culture and its charitable organization — Science, Theology and the Ontological Quest (STOQ), an alliance of experts from the disciplines of science, theology, and philosophy. The purpose of this collaboration is to promote and conduct an interdisciplinary dialogue to build a bridge between science and theology. This union also is intended to expand research and raise awareness about adult stem cell therapies and explore their clinical applications in the field of regenerative medicine as well as the cultural impact of such research. Smith shares her insights on the purpose and process of brokering a deal with a religious organization, something many scientists might view with skepticism.

IT'S NOT ABOUT RELIGION

When Francis Collins, M.D., Ph.D., was nominated for the position of NIH director in 2009, some members of the scientific community publicly questioned how Collins, an avowed Christian, could lead the NIH when his faith positioned him as an advocate of profoundly antiscientific beliefs. NeoStem's Smith has faced similar controversy. In 2011, UC Davis School of Medicine associate professor Paul Knoepfler, Ph.D., described the collaboration between the Vatican and NeoStem as a $1 million gamble, questioning the mixing of science and religion. "To shy away from a certain group that has an incredible influence on over a billion people because its religious beliefs are different than yours, just doesn't make sense," Smith states. "It is not about religion, nor my religious beliefs. This is about education."

According to Smith, there is a tremendous amount of confusion between the types of stem cell research being conducted. "If you look at the progress that's been made over the last 10 years, people really don't get it," she states. "They don't understand how much progress has been made using adult stem cells as the source of cells. Today there are 4,600 adult stem cell trials and only 26 embryonic." Further, Smith notes, many followers of the Catholic Church don't realize the Vatican is not opposed to adult stem cell research and even stem cell research involving fetuses that have been spontaneously aborted. Smith believed a collaboration with the Vatican could help clear up some of the confusion and misinformation around stem cell research, which would be in the best interest of those looking for cures for chronic diseases and NeoStem shareholders. Fostering that kind of understanding would also help to meet the stated objectives of the Stem for Life Foundation (SFLF) — raising public awareness of adult stem cell therapies and supporting adult stem cell R&D. But before the Vatican and NeoStem could embark on the task of educating the 1 billion+ followers of the Roman Catholic Church on stem cell research, they first needed to become educated about each other. "After the first meeting, I sent representatives of the church home with 80 articles on stem cells," she explains. Smith, who is Jewish, also went out and bought *Catholicism for Dummies* by Rev. John Trigilio Jr. and Rev. Kenneth Brighenti. "There are things they don't believe in, such as IVF [*in vitro* fertilization], and so it's important to understand their sensitivities," she states. The process of due diligence on the part of all collaborators, from the initial meeting to the signing of an agreement, took about five months — a fairly quick process when you consider the conservative nature of the parties involved. Dr. Smith noted the process of creating the collaboration moved much more quickly when compared to discussions NeoStem has had with large pharma companies and other industry partners. "With strategic partnerships," says Smith, "it takes time to find the right fit, at the right time, with the right budget cycle." She says in the case of a strategic partnership, one party is usually asking for something, while the other gets something, which can take time to negotiate. With the Vatican collaboration, there was no real negotiation. "We set forth with what we wanted to accomplish, how we could do it together, and put it on paper," Smith states. At the top of Smith's list of keys to moving the process along she placed trust. "They had to get comfortable we would not do something that would be in opposition to their faith," she states. "They really trusted us to respect their beliefs." Second on the list was communication, closely followed by goals. With the primary goal being education, the collaborators began to set out how to go about educating.

THE MISSION OF EDUCATION

The education process not only involved teaching the followers of the Catholic Church about adult

stem cell research, but helping thought leaders of science and theology gain an understanding of one another. One of the best mechanisms by which to do this is through a conference with "open dialogue." It took about a year and a half to put together the first conference, held at the Vatican, Nov. 9-11, 2011, and titled, "Adult Stem Cells: Science and the Future of Man and Culture." It included adult stem cell research experts, recognized leaders in life sciences, medicine, religion, ethics, public policy, as well as CBS award-winning medical broadcast journalist, Max Gomez, Ph.D. "We felt that if we could get a statement from the pope during the event saying he supports adult stem cell therapies, people would truly believe the Catholic Church was supportive of this science, which would be monumental," says Smith in regard to gaining buy-in from the masses. "We told the pope we intended to write a book as another component of the educational process." Entitled, *The Healing Cell: How the Greatest Revolution in Medicine Is Changing Your Life*, the book is co-authored by Smith, with Monsignor Tomasz Trafny and Max Gomez. It also includes a foreword by Gianfranco Cardinal Ravasi, president of the Pontifical Council for Culture, and an address by Pope Benedict XVI, which states, "In general, no such ethical problems arise when stem cells are taken from the tissues of an adult organism, from the blood of the umbilical cord at the moment of birth, or from fetuses who have died of natural causes." This type of statement from the pope is exactly what the collaboration team hoped would move their educational initiative forward.

The book, published April 2, 2013, was followed by the second international educational conference at the Vatican. Building upon the success of the previous conference, this year's tripled in the number of attendees and included correspondents from the *Wall Street Journal*, CBS, NBC, and Fox, actual stem cell patients, top-level researchers from the likes of the Dana-Farber Cancer Institute and the University of Texas MD Anderson Cancer Center, as well as numerous industry executives from such well-known companies as Pfizer and Celgene. "We also brought students in from around the world via a student ambassador program, to create a bigger education platform," states Smith. "Not only do we have to educate church leaders and individuals, but you have the whole secondary process to help the next generation of thought leaders understand the science, misconceptions, and the various issues surrounding stem cell research."

According to Smith, the collaboration has set its sights on milestones around electronic media, e-learning, DVDs, and social media. The collaboration also would like to raise money to help fund stem cell research. "Until investors see there is a pathway to commercialization and a clear regulatory pathway to approval, funding will not be plentiful," she affirms. "In the meantime, we need to look for support through foundations, grants, and philanthropic money and create a forum for funding these programs." Smith believes the collaboration a success, pointing to the fact that even with the changing of the pope from Benedict XVI to Pope Francis, the partnership was extended through 2020.

NeoStem's CEO has had a busy year, co-authoring and publishing a book, moving the company from trading on the NYSE to the NASDAQ, brokering an agreement with the Vatican, hiring a new CFO, CMO, and executive vice president, and receiving a Key Founder's Award from the Vatican. Investors have been taking notice of Smith's efforts. With the stock trading around its 52-week high of just under $10 (at the time of this writing), some analysts are anticipating an even greater upside, especially if the company gets good news on AMR-001, a treatment targeting patients at risk from congestive heart failure, significant arrhythmias, premature death, and acute coronary syndrome — a $1.2 billion market.

IS MIXING RELIGION AND SCIENCE A GOOD IDEA?

According to the University of Maryland Medical Center, a growing number of studies reveal that spirituality may play a bigger role in the healing process than previously thought. Qualities like faith, hope, forgiveness, and the use of social support and prayer seem to have a noticeable effect on health and healing. For example, a 35-year clinical study of Harvard graduates revealed that graduates who expressed hope and optimism lived longer and had fewer illnesses in their lifetime. Results from several studies indicate that people with strong religious and spiritual beliefs heal faster from surgery, are less anxious and depressed, have lower blood pressure, and cope better with chronic illnesses. "When people have a health illness, they either go to religion or reject it," says Robin Smith, M.D., the chairman and CEO of NeoStem. Some may argue that spirituality or prayer in treatment is merely a placebo effect. They may be right.

In the January-February 2013 issue of *Harvard Magazine,* Ted Kaptchuk, a professor of medicine at Harvard Medical School and the director of the Harvard-wide Program in Placebo Studies and the Therapeutic Encounter (PiPS), reported a very interesting finding just two weeks into a randomized clinical drug trial. Nearly a third of the 270 subjects complained of awful side effects. All of the subjects had enrolled in the study hoping to alleviate severe arm pain. In one part of the study, half of the subjects received pain-reducing pills; the others were offered acupuncture to alleviate the pain. In both cases, people began calling in complaining of side effects, which just so happened to be the same as the side effects they had been warned the treatment would produce. More astoundingly, other patients reported real relief, and those who received acupuncture felt better than those on the anti-pain pill. No study had ever proven acupuncture to be superior to painkillers — neither did Kaptchuk's. Here's why. The pills were placebos consisting of cornstarch. The acupuncture needles were retractable shams that never pierced the skin. The study was designed to compare two fakes. Researchers have found that placebo treatments can stimulate real physiological responses, and thus why one of the key components to gaining drug approval is proven superiority of an active medication over placebo. According to Kaptchuk, the challenge now is to uncover the mechanisms behind these physiological responses – what is happening in our bodies, brains, in the method of delivery (e.g. needle versus pill), in the room where placebo treatments are administered (e.g. calming physical surroundings, caring versus curt doctor) — because the effect is actually many effects woven together. While at it, perhaps researchers should investigate spirituality's impact on the placebo effect. Rather than trying to separate science and religion, let's take a closer look as to how they may, or may not be, inextricably intertwined.

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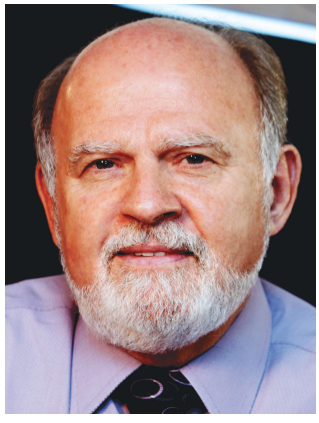
COMPETING IN THE RARE DISEASE SPACE

BY CINDY DUBIN, CONTRIBUTING EDITOR



"As a foundation, we can recruit for a Phase 3 pivotal study within 6 to 10 weeks. That's why we have been able to get companies like CSL Behring to focus on developing therapies for Alpha-1," says John Walsh, president and CEO of the Alpha-1 Foundation.

There are approximately 7,000 different types of rare diseases and disorders affecting an estimated 350 million people worldwide. Because these diseases are so diverse and complex, there are inherent gaps that exist in patient treatment. The Rare Disease Impact Report illustrates that it takes an average of seven years for a patient with a rare disease in the United States to receive a proper diagnosis. On the journey to diagnosis, a patient typically visits up to eight different physicians and receives two to three misdiagnoses.

CSL Behring began carving out its niche in the rare disease space about 25 years ago, focusing on plasma-derived proteins (PDPs). PDPs are used to treat rare and serious diseases that include coagulation disorders such as hemophilia and immune deficiencies, Alpha-1 antitrypsin deficiency, hereditary angioedema (HAE), and hemolytic disease in newborns.

At that time, CSL was the lone fish in a small pond. Today, the global provider of plasma-derived and recombinant factor products is up against a handful of competitors in a space estimated to be worth more than $15 billion annually. As previously reported by Life Science Leader magazine (see September 2009 issue, "Lessons Learned From PDP Market Success"), industry experts expect the size of the market to continue to steadily grow and potentially exceed $32 billion per year by 2016.

"In the rare disease arena, there is generally a lower cost of development and the promise of patent protection, so it becomes evident that a company can realize a certain degree of profitability under the right circumstances," says Russell Basser, senior VP of global clinical research and development at CSL Behring. "This tends to attract more companies to the space."

Consider the hemophilia sector. Basser explains that there was a flurry of recombinant factor development and launches after the contamination issues in the late 1980s with several recombinants hitting the market. Yet, prior to that, little or no technological progress had been made for 25 years. But, in the last five or

six years, he says, competition has picked up, and the market is now worth about $10 billion.

A similar story is unfolding in the HAE space. According to Basser, CSL held the title of being the only company in the world to offer a product to treat HAE, and things remained that way for 15 years. According to the Orphan Druganaut Blog, there are now a handful of similarly licensed products for HAE, a space valued at about $113.8 million in 2011 and expected to reach $385 million in 2019.

"It's interesting how the rare disease space is becoming so crowded," reflects Basser. "We all have to be that much smarter about how we do business, and it puts more pressure on drug development as we are a few players vying for the same patients and skilled personnel."

EMBRACE THE SPACE

With a feeding frenzy under way in the rare disease drug-development sector, staying ahead of the competition requires a focused commitment. "Considering we are now surrounded by competitors in HAE, we have had to strengthen our focus even more," says Basser.

To remain focused, CSL Behring has formed close relationships with patient advocacy groups. These organizations educate patients and family members about a given rare disease: how to seek a diagnosis, and how to gain access to treatment. Some groups are disease-specific while others are umbrella organizations, such as the European Organization for Rare Diseases (EURODIS) and the National Organization for Rare Disorders (NORD). CSL works with both types of organizations to ensure patients have access to appropriate therapies. "The secondary gain becomes obvious in that we have the therapies the patients need, and we want them to use them," explains Basser.

Engaging with patient groups also helps ensure that diseases don't go underappreciated or misdiagnosed, he says. "We understand that having one of these diseases can be isolating, but a misdiagnosis can lead to death. We are working with the groups to improve the rates of accurate diagnosis and the proper choice of treatments."

CSL also uses social media to spread its message about treating rare diseases. Basser explains that tapping into online groups enables the company to provide education about treatments as well as information regarding what trials are occurring in a patient's region. The goal is to empower the patients. CSL has also set up specific Web pages and YouTube videos to do the same.

"Engaging with patient advocacy groups isn't unique, but I think we do it as well as anyone who competes in our disease areas," says Basser. "We give support to patients beyond getting them to use our product. It's about embracing the entire opportunity. That's why we've been successful."

ENLIST PATIENTS

Patient advocacy groups are also playing a larger role in designing clinical trials. These groups help to make sure the drugs are valuable for the patients from a regulatory and medical perspective as well as from a patient perspective. The challenge with rare diseases is that only a small number of individuals are available to participate in a clinical study. In order for a disease to be qualified in the U.S. as "rare," the afflicted patient pool needs to be fewer than 200,000 individuals. So, a patient advocacy group can really help recruit patients.

This has not gone unnoticed by CSL. The company has teamed up with several advocacy groups, including the Alpha-1 Foundation, a not-for-profit Florida corporation cofounded by John Walsh in 1995, for individuals diagnosed with Alpha-1 antitrypsin deficiency, also known as genetic COPD. When someone is diagnosed with Alpha-1, that person is automatically asked to enroll in the Alpha-1 research registry and connected with a clinical resource center doing trials and studies. In fact, the Alpha-1 Foundation was the result of a seven-year Alpha-1 progression study being conducted by the NIH.

"Those of us who participated in that study realized the value of participating in clinical research," explains Walsh, who is also president and CEO of the foundation. "As a founda-

> **"It's interesting how the rare disease space is becoming so crowded. We all have to be that much smarter about how we do business, and it puts more pressure on drug development."**
>
> Russell Basser, senior VP of global clinical research and development, CSL Behring

tion, we can recruit for a Phase 3 pivotal study within 6 to 10 weeks. That's why we have been able to get companies like CSL Behring to focus on developing therapies for Alpha-1."

One of those therapies is Zemaira, an Alpha-1 proteinase inhibitor developed about 10 years ago by CSL Behring. This augmentation therapy replaces the missing protein in people who have Alpha-1 deficiency. CSL asked the Alpha-1 Foundation to participate in the design of the clinical trial protocols and to be involved with FDA discussions in getting the Zemaira trial design approved.

"Having a patient advocacy group at the table brings a completely new perspective that the FDA wouldn't have otherwise," says Walsh. "We actually challenged a reviewer on the number of bronchoscopies that would be given and the number of patients to whom it would be given. And the FDA backed off. The importance of being at the table with the sponsor of a drug trial adds tremendous value because the FDA gets a completely different perspective on the potential impact of the clinical protocol."

Zemaira was ultimately approved by the FDA as an injectable therapy for patients suffering from Alpha-1 and is among a handful of such therapies.

"It is critically important for individuals afflicted with rare diseases to be involved with clinical research," says Walsh. "Without the patients, the research won't get done. As a whole, I think the pharmaceutical industry is realizing the importance of getting patients involved with clinical studies."

In fact, the FDA is promoting opportunities for patient advocacy earlier in the policymaking process than has been the case historically. The FDA Safety and Innovation Act (enacted in mid-2012) mandates the involvement of patient representatives in roles beyond those of the advisory committees. Draft procedures for patient involvement were made public in September.

Both Walsh and Basser agree that the mandate will be embraced by patients and will accelerate therapies. "In the future, we will need to think more about how we engage patients in the design of a trial program," says Basser.

EDUCATE THE TRIAL SITES

Just as patients are essential to the success of a clinical trial, so too are the investigator sites. Basser explains that it is important that the sites are engaged and that a coordinated effort be made to ensure the investigators really understand the complicated protocols. "As our success and portfolio have grown over the years, we have had to learn to engage the sites in a much more intimate way."

This, he adds, is necessary because every patient counts in studies in rare disease. "We have many studies where we expect each site to recruit only one or two patients. This has a number of implications. For starters, we need to work closely with our study investigators to ensure they identify every potentially eligible patient in their clinics. We must also cast a wide net for patients and often work with investigators who have a lot of expertise in the particular rare disease but limited experience in clinical trials. Finally, there is a very steep learning curve for the site teams as the first patient they treat might be the only one."

So, CSL has learned to stay close to the study coordinators and investigators to get patients into the trials and make sure the quality of the data is adequate. For example, when investigators sign up for a trial, they must learn and understand the process and the protocol, but ultimately, the sponsor has a responsibility to ensure the trial is conducted according to good clinical practice guidelines and that the data is accurate. That's especially important considering the sponsor wants to use that data when getting approval from a federal regulatory agency.

Basser explains that if investigators are going to sign up for a trial, it's up to them to learn and understand all aspects of the trial, "But in the end, we're the ones who have the most in the game. If they don't follow the protocol appropriately, we get data that we can't use. Then, the product might not get licensed. It's our responsibility to ensure investigators are trained adequately."

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Financial Metrics For Brand Protection

by Ron Guido

Many companies struggle with the need to justify investments in anticounterfeiting programs. Others deem it an important part of their business rationale to help safeguard key brands; yet they question how to devise such metrics. I feel strongly that a credible scorecard can be produced, even for the ostensibly intangible results associated with combatting illicit trade.

By measuring the financial effects of brand-protection programs and their secondary impacts on operational efficiencies and effectiveness, your company will generate the management information needed to:

- monitor the integrity of your supply chain over time in financial terms
- quantify breaches in the supply chain that may endanger patients/customers
- measure the potential impact of future supply chain breaches (lost revenue or increased costs)
- objectively inform management of benefits derived from investments in supply chain security (ROI).

Along with ongoing monitoring programs, combined with analysis of your own commercial data, a brand-protection financial scorecard is a valuable tool in your continuing efforts to fulfill your company's promise to your patients to deliver safe medicines. In doing so, you enhance the reputation and the profitability of your businesses around the globe.

A sustainable process can be created to capture the financial benefits of brand-protection programs and counterfeiting countermeasures across all functional areas, regions, and product lines of your company. Such information can be captured and reported by brand, channel of trade, or type of violation. With the accent on both "recovery" from past/current insults and "prevention" or "loss avoidance," this process divides reported results into two categories: recovery and avoidance.

RECOVERY

The concept of revenue recovery, as the phrase implies, is to recognize that you, the IP rights holder and brand owner, have created a finite amount of market demand for your product. That brand would therefore generate an expected level of sales against the pent-up demand. Yet some of that revenue has been "hijacked" by counterfeiters purporting their fakes to be genuine. Therefore, if you determine that your brand-protection programs have had a direct effect on retarding the sales of counterfeited products in a targeted market or channel, then you have earned the value of that recovery. In other words, if you did nothing to thwart counterfeit trade of your brands, your sales would be booked by those operating outside the legitimate supply chain, tantamount to losing market share to a clandestine competitor. On the other hand, recovering sales lost to illicit traders provides the basis for assigning financial value to the ways and means of anticounterfeiting processes and technologies.

Recovery also can take the form of nonrevenue-related reclamation of value. If, for instance, your company pursued civil damages against convicted counterfeiters, your monetary award can be included in the recovery bucket. (Note: Some organizations opt to record recovery dollars net of the costs, e.g. legal fees.) Some examples of activities that generate brand-protection recovery results are shown in sidebar 1.

AVOIDANCE

Unlike recovery, which recognizes insults to brand integrity after the fact, brand protection measures of avoidance are derived from estimates of the likelihood of a brand violation if no preventive actions are taken. Given the dearth of available information about counterfeit and gray market transactions, avoidance measures must be associated with rates of illicit trade titrated from known aggregate data or from market surveys (sampling) conducted to size the problem. For example, if your branded drug is in the lifestyle category (e.g. erectile dysfunction), your financial scorecard may assume that your drug will experience a similar rate of counterfeiting to the published data of Viagra, tempered by market share, price differences, and adoption rates. Alternately, you may elect to precede your anticounterfeiting

implementation efforts with a statistically relevant survey of the affected market and, using authentication methods, determine the prevalence of fakes in the market. Following the implementation of supply chain best practices and/or application of anticounterfeiting technologies, a similarly powered field survey will provide an estimate of the financial benefit associated with your risk-mitigating efforts. But there is a catch to this predictive analysis of counterfeit drugs. If your product is found to be counterfeited in a certain market postimplementation, then it is prudent to reset the savings to zero for an agreed-upon period of time (e.g. one year) in the specific market or region where the fake was discovered. In effect, your financial scorecard should be debited for ineffective brand-protection activities.

Beyond avoidance of market losses, the brand-protection financials should include operational gains resulting from safeguards that generate collateral (secondary) benefits to the organization. This category of value emanates from the con-

SIDEBAR 1:

BRAND PROTECTION FINANCIAL RECOVERY ACTIVITIES

1. Determine market value of products seized in transit or from unauthorized channels — includes recovery of counterfeit, diverted, and stolen goods.
2. File civil suit against convicted counterfeiters and claim litigation awards (legal recovery).
3. Take down rogue Internet sites and estimate value of sales redirected to legitimate channels (short-term benefit).
4. Conduct IP protection interventions through law enforcement agents and customs agents — capture market value of seized goods.

SIDEBAR 2:

BRAND-PROTECTION FINANCIAL AVOIDANCE ACTIVITIES

1. New products introduced include anticounterfeiting technologies. Calculate the revenue loss avoided by using estimates of predicted levels of fake goods present in the market. Make assumptions based upon the general product category (e.g. lifestyle or oncology drugs), market risk (channels and countries of sale), and unit price.

2. Implement and adopt supply chain best practices. A market value is assigned to implementation of each practice with appropriate lag times for old inventory flow-through.

3. Reduce insurance premiums via installation of facility or cargo security upgrades.

4. Realize operational efficiency gains by improving the transparency and control of finished goods. These include documented improvements in:
   - supply/demand balancing
   - expiry date management
   - returns processing/integrity
   - recalls and market retrieval effectiveness
   - new-product tracking
   - in-transit and storage theft avoidance
   - chargebacks/rebates: reduced labor and reconciliation time

cept that the legitimate supply chain is being violated, in part, due to the limited visibility and control of the manufacturer via downstream supply chain transactions. Beyond wholesalers, the pharmaceutical supply chain (which is more of a network than a linear chain) lacks real-time tracking of doses, i.e. electronic pedigree. Typically, when supply integrity practices are applied to routine supply chain functions, there is a fundamental increase in awareness of transactions and more control over inventory. The resulting operational effectiveness and efficiency gains can be allocated, in part, to investments in brand protection. Some examples of activities which generate brand-protection avoidance results are shown in sidebar 2.

REPORTING/ VALIDATION PROCESS

The governance of the financial scorecard results should be managed by the finance/accounting department with buy-in from marketing and supply chain management. Results will be accumulated within the brand-protection team on an ongoing basis, tabulated monthly, and reported by finance/accounting quarterly to minimize reversals of entries due to premature or overzealous recording of information.

To secure credibility in the use of these metrics over time, it is important to use conservative approaches for reporting results. Keep in mind that the value of "scorecarding" your brand-protection performance results lies in a) tracking macro measures of return on investment, b) showing trends in performance over time and, most importantly c) rallying the organization to become more accountable for supply integrity.

> A brand-protection financial scorecard is a valuable tool in your continuing efforts to fulfill your company's promise to your patients to deliver safe medicines.

In summary, encouraged by globalization of commerce, broader manufacturing footprints in high-risk markets, and the profitability of popular brands in a sluggish economy, counterfeiters are experiencing unprecedented success in falsifying prescription medicines. It is incumbent upon brand owners to incorporate brand-protection practices into their commercial strategies. It is equally important for supply chain executives to seek additional operational gains from increased transparency and control of downstream transactions. Together, these goals can be realized by selective investments in brand-protection programs and technologies.

The immeasurable value of increasing patient safety notwithstanding, life science leaders should adopt objective metrics to gauge the effectiveness of investments in anticounterfeiting activities. These metrics will galvanize your organization around the value of brand-protection safeguards and help fulfill the trust mark of your brands. Your patients will thank you.

About the Author

Ron Guido is the president of Lifecare Services, LLC, a management-consulting firm specializing in healthcare marketing, brand protection, and strategic planning. He has more than 36 years of experience in the healthcare industry and is the former vice president of brand protection at Johnson & Johnson.

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Crowdfunding And The Life Sciences: Will It Work?

By Cliff Mintz, Ph.D., contributing editor

The past five years have been one of the most difficult periods for raising capital in the life sciences industry. The recession — coupled with longer drug and devices approval times, higher than normal rate of drug failures, and a challenging regulatory environment — has contributed to a scarcity of venture monies available to start-ups and early-stage life sciences companies.

"Over the past few years, venture capitalists have primarily invested in later-stage, risk-mitigated companies and, as an industry, backed away from funding creative ideas or early-stage companies where they have historically invested," said Steven Burrill, CEO of Burrill & Company, a life sciences venture capital and private equity company.

This shift has forced many would-be entrepreneurs and early-stage life sciences companies to consider nontraditional funding options, including crowdfunding, to start up operations or advance drug/device development programs.

WHAT IS CROWDFUNDING?

With crowdfunding, you use the Internet to donate, loan, or invest money in a new company, idea, or project. It has been popularized by websites such as Kickstarter, Indiegogo, RocketHub, and others that have been successfully used to fund development of software, consumer products, art projects, films, civic efforts, and even political campaigns.

Generally speaking, there are two types of crowdfunding: donations/rewards and equity. In the donations/rewards model, pioneered by Kickstarter and Indiegogo, investors either donate money to a project for altruistic reasons (e.g. to develop a treatment to cure a disease) or because they receive a reward (t-shirt, early access to a product, product discounts, etc.) in exchange for their investment.

In contrast, in the equity crowdsourcing model, contributors receive an ownership interest or shareholder stake in a business/entity collecting the funds. Because of this, the investment is considered a "security" under federal and state laws and is regulated by the U.S. Securities and Exchange Commission (SEC). While donation/rewards crowdfunding has been in existence for the past several years, equity crowdfunding was not possible until April 2012 when the JOBS Act (Jumpstart Our Business Startups Act) was signed into law.

The JOBS Act contains a provision for equity crowdfunding (Capital Raising Online While Deterring Fraud and Unethical Non-Disclosure Act or CROWDFUND Act), which allows companies to raise capital in small amounts from large groups of people using the Internet and social media. Equity crowdsourcing is not widespread because the SEC is still working out the regulations for its implementation. However, equity crowdfunding experts believe the aggregate amount sold to equity investors through an investment-based portal (approved by the SEC) in any 12-month period may not exceed $1 million. Also, it is likely that individual investors will have monetary caps placed on their equity investments made through these investment portals.

HOW CROWDFUNDING WORKS

Like traditional fundraising, companies or individuals seeking financing craft a "pitch," an executive summary that describes why the funding is necessary and what the funds will be used for. The pitch (and other supplementary information) is published on a crowdfunding portal along with a financial goal. For example, a company may be seeking $1 million for new product development. Typically, companies or individuals are required to reach their funding goal, or investors get their money back.

The portal hosting the campaigns keeps a percentage of what is invested or donated — usually 7 to 20 percent. Sometimes a flat fee is charged.

The reason why crowdfunding appeals to many would-be investors is the amount of transparency associated with fundraising campaigns. In most instances, the progress of the campaigns (and expected company milestones) is prominently displayed on the portal and easily accessible to both investors and donors. Also, because individual investors usually do not invest substantial sums of money, the amount of risk involved in financing crowdfunded campaigns is generally very low.

At present, there are eight crowdfunding portals operating in the U.S. (table 1 on page 52). Of these, five are donations/rewards portals, and the remaining three platforms are based on the equity-based financing model.

DONATIONS/REWARDS CROWDFUNDING PORTALS

Medstartr (www.medstartr.com), one of the earliest donations/rewards portals, mainly focuses on healthcare, including medical devices, health IT software development, and digital-health applications.

Alex Fair created the platform with Mike Pence (former lead developer for Kickstarter) after he failed to capitalize a healthcare venture using conventional fundraising channels. "I tried to set up a campaign on Kickstarter and found out they do not support healthcare fundraising. After a bit of research, Mike and I decided to create a crowdfunding platform exclusively designed for healthcare projects" said Fair.

Since its inception in early 2012, Medstartr has helped finance numerous healthcare projects with an average raised of $13,100 per campaign. While the monies raised on the Medstartr platform are usually not large, Fair believes that the funds allow entrepreneurs and earlier-stage companies to continue to innovate and ultimately succeed. "A successful campaign on Medstartr can help to validate an idea or project and engage external investors who may have the resources to invest in subsequent financing rounds," offered Fair. He added, "Before Medstartr, it was very difficult to get market validation of lots of good ideas and products in the healthcare space, which ultimately prevented them from reaching the market."

In addition to Medstartr, there are several donation/rewards portals that help scientists raise funds to support specific science research projects (table 1). Of these, Microryza (www.microryza.com/), founded by Cynthia Wu and Deny Luan, two Ph.D.-trained biomedical scientists, mainly focuses on funding investigator-initiated life sciences research.

The concept for the Microryza portal began when Wu was unable to secure funding during her Ph.D. work for a research project she wanted to pursue. "I had this great idea that was very risky, and I knew that it would never be funded by an NIH grant, so I started thinking about a Kickstarter-type site for life sciences projects," said Wu. After interviewing over 100 scientists to confirm that other researchers had high-risk projects with little hope of funding, Wu and Luan launched Microryza in April 2012.

At present, Microryza launches approximately 12 campaigns per week after the projects undergo a rigorous screening process. Like Medstartr, the amount of money raised per Microryza campaign is usually not large (usually several thousands of dollars). Nevertheless, Wu is convinced that Microryza will help to "better inform the public about scientific research and how it is conducted" and to identify

Table 1:

Name	Principal(s)	Sector	Crowdfunding Type	Website
Medstartr	Alex Fair, Mike Pence	healthcare, medical devices, digital health	donation/rewards	medstartr.com
Health Tech Hatch	Pat Salber, M.D.	healthcare	donation/rewards	healthtechhatch.com
Microryza	Cindy Wu, Ph.D./ Deny Luan, Ph.D.	biomedical and life sciences research	donation/rewards	microryza.com
IAmScientist	Borya Shakhnovich, Ph.D./ Claude Sheer	biomedical and life sciences research and other scientific disciplines	donation/rewards	knowledgexchange.iamscientist.com
Petridish	Matt Salzberg/Ilia Papas	biomedical and life sciences research and other scientific disciplines	donation/rewards	www.petridish.org
Poliwogg	Gregory Simon	healthcare and biotech	equity	corporate.poliwogg.com
Healthfundr	Jared Iverson, J.D./Sean Schantzen, J.D./Kerry Lowder, M.D.	biotech, medical devices, and healthcare	equity	healthfundr.com
VentureHealth	Mir Imran/Andrew Farquharson	biotech, medical devices, healthcare, and digital health	equity	www.venturehealth.com

potential new "science patrons" interested in making an investment in the "$160 billion-dollar U.S. market of unfunded research projects."

EQUITY CROWDFUNDING PORTALS

Prior to passage of the JOBS Act, life sciences crowdfunding portals had to be built and operated using the donations/rewards financing model. However, over the past year since passage of the act, three crowdfunding portals built on equity-based financing have emerged.

Healthfundr (healthfundr.com) was launched in May 2013 by Jared Iverson and Sean Schantzen, two attorneys with extensive backgrounds in raising capital for life sciences ventures. The Healthfundr portal is designed to help private, early-stage healthcare companies raise $2 million to $5 million through an equity-based crowdfunding mechanism.

Although the JOBS Act legalized equity crowdfunding, Schantzen believes the $1 million annual crowdfunding investment cap will not meet the capital needs of many life sciences companies. "Most life sciences companies are not going to be able to get by with just a million dollars in capital a year, if you use the 10 year/$150 million life sciences commercialization costs model," said Schantzen.

Instead, Healthfundr intends to use its crowdfunding portal as sort of a matchmaking platform for companies it selects to showcase (2 to 4 percent of applicants) and appropriate pools of investors registered at the site. Schantzen notes that Healthfundr doesn't make recommendations for investors; it just makes opportunities available to them. "Investors must decide for themselves whether or not an investment is right for them," emphasized Schantzen.

Unlike many of the donation/rewards crowdfunding sites that depend on portal volume, Healthfundr intends to work with only a handful of companies at a time. "We are a highly selective, curated portal and want to work on a small number of deals that we personally believe in and are a good fit for our funding model," said Iverson, Healthfundr's CEO.

CHALLENGES

While many healthcare and biotech entrepreneurs are very excited by the prospects of life sciences crowdfunding opportunities, there are a substantial number of challenges — mainly with equity-based crowdfunding — that must be addressed before this new funding paradigm can be validated.

First, the SEC has yet to release the regulations that lay the groundwork for equity crowdfunding. In the absence of these regulations, only accredited investors, not the general public, can invest using equity-based crowdfunding portals. However, many crowdfunding experts expect the regulations to be released sometime in 2014. But it is generally assumed that it will be many months before the SEC establishes formal procedures for registering portals and issuers.

Second, companies that use equity crowdfunding portals will not be allowed to send out mass solicitations to prospective investors at will. The JOBS Act stipulates that equity-based crowdfunding can only be conducted through brokers or portals registered with the SEC. This may actually limit fundraising opportunities. Also, companies that raise between $100,000 and $500,000 via an equity crowdsourcing portal will be required by the JOBS Act to have their financial statements reviewed by an independent certified public account. Companies that raise funds in excess of $500,000 are required to have audited financial statements. Both of these accounting services can be costly and are not typically required of companies that raise less than $1 million through conventional funding mechanisms. Finally, once a crowdfunding offering closes, companies will be required to annually file financial statements with the SEC and compile annual investor reports for its shareholders. Complying with these regulatory requirements may be burdensome for most start-ups, especially for those that raise less than $1 million.

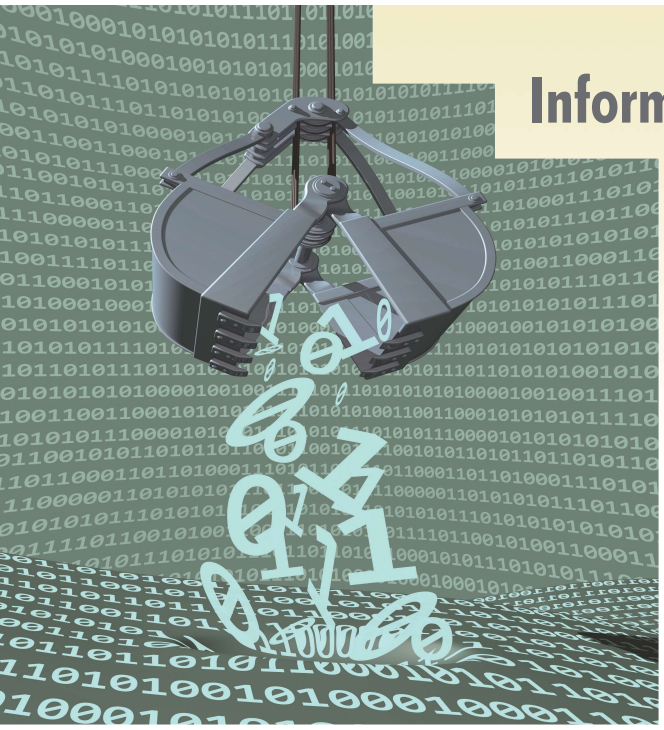
Third, as previously mentioned, the aggregate amount sold to equity investors through a crowdfunding portal in any 12-month period cannot exceed $1 million. Individual investors will also have caps placed on equity investments made through equity crowdfunding portals. Consequently, it is not clear whether or not equity-based crowdfunding will be able to provide early-stage biotech/devices companies with the required amounts of capital they need.

Finally, concerns have been raised about the high fees that may be associated with equity-based crowdfunding portals. Some experts believe that usage fees may be upwards of 10 to 20 percent because of broker/portal registration costs and exhaustive due diligence that must be conducted before company offerings can be posted to the portal. Also, the larger than normal number of shareholders who are likely to invest in a company that uses a crowdfunding portal may interfere with raising additional rounds of capital. In many states, corporate law stipulates that shareholder approval is required before a company can accept additional funding. Getting large number of shareholders to agree to and approve subsequent rounds of funding may be difficult and ultimately interfere with the long-term financial viability of a company.

WHAT DOES THE FUTURE HOLD?

Many venture capital and private equity professionals, such as Seth Yakatan of Katan Associates, believe that crowdfunding will be good for the life sciences industry. "It has the ability to broaden the audience of potential investors and provides a really great venue for smaller projects and earlier-stage companies to leverage the power of social media and mass appeal for a cause," said Yakatan. Likewise, Steve Burrill believes that crowdsourcing will continue to promote innovation and ultimately play a role in life sciences fundraising. Burrill said, "Crowdfunding will not solve early-stage capital demand, but it will make a contribution to the life sciences sector."

While it is too early to determine if crowdfunding will have an impact on the life sciences industry, Medstartr's Fair offered an insightful comment about the potential of crowdfunding. "If you want to go fast, then do it by yourself, but if you want to go far, then go with the crowd." On the other hand, Burrill quipped, "We live in a world where everyone wants to push buttons, but life sciences fundraising is still a contact sport!"



Digging For Big Data Gold: Data Mining As A Route To Drug Development Success

By Suzanne Elvidge, contributing editor

The term Big Data is on everyone's lips, from retailers to healthcare providers. But what actually is it, and how can it help biopharma R&D? There are many definitions of Big Data, but perhaps the simplest is a collection of data that's approximately bigger than one terabyte and/or is too big to handle using standard software and analytical processes.

Big Data is becoming a major part of all facets of healthcare as physicians' notes on patients, test results, prescription records, and even imaging results (e.g. X-rays, MRIs) are being included in electronic medical records (EMRs). There are many electronic public databases that are part of biobanks and national healthcare studies. In addition, more and more clinical trial results and other drug development and approval documents are being stored electronically.

PICKING OUT THE NUGGETS OF DATA

Drug development costs are skyrocketing, and despite this, attrition rates continue to climb with drugs still failing in late-stage clinical trials. Accessing this treasure trove of Big Data could help by improving compound selection and refining clinical trials. But how to find the gold among the dross?

"The challenge of Big Data is the number of combinations of factors involved. For example, if you have 1,000 patients, you could have 1,000 genomes, 1,000 sets of comorbidities, 1,000 phenotypes — the list could go on," says Steve Gardner, partner at Biolauncher, a United Kingdom-based biopharma consultancy. It's situations like this where data mining, which uses software algorithms to analyze and summarize the data, comes to the rescue. GenoKey, which provides analytics solutions for healthcare Big Data, has developed an array-based technology to solve very large combinatorial problems in case-control data, finding patterns in the data using massively parallel GPU processing.

NuMedii, a start-up based in Menlo Park, CA, is using data mining to correlate disease information and drug data to predict drug efficacy. The company's database includes billions of points of disease, pharmacological, and clinical data, and it mines this using network-based algorithms. This should de-risk the development process, increasing the chance of drugs making it through to the market.

The U.K. start-up MedChemica is at the core of a collaboration designed to speed drug development using data mining of precompetitive-shared data while maintaining the security of each individual partner's intellectual property. As Hans-Joachim Boehm, head of small molecule research at Roche (one of MedChemica's collaborators), explains, the driver behind the collaboration was that many companies have a lot of preclinical data, but the challenge is how to analyze it and make practical use of it.

"Drug development is an iterative process, and you learn at each stage. You start with a target and a molecule that hits the target. You then characterize the interaction and the molecule, find out what the activity and the issues are, and then make modifications, creating a new molecule. Then you start the process again," Boehm says.

This is a time-consuming process and generates a lot of data. The collaboration, based on MedChemica's matched molecular pair analysis technology, aims to make it more efficient, using existing information to reduce the number of steps between hit and candidate. MedChemica's algorithms mine the partners' databases of molecules generated during the iterative process to find pairs that are very closely matched. The software then analyzes the differences between the *in vitro* data from the pairs of molecules and maps this to the structural changes in the molecules. The output from the analysis is then used to create rules that can be applied to virtual molecules to predict the impacts of similar structural changes. When drugs fail at a late stage of development, it's generally because of safety issues, and so toxicity data is particularly valuable to be able to "design out" issues at a much earlier stage.

"We originally created the matched molecular pairs technology at AstraZeneca. However, this is a very data-hungry process, and we realized that there just wouldn't be enough data in any one individual company. MedChemica was formed as a neutral intermediary with the idea of bringing multiple companies together

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and acting as the hub of the consortium, and AstraZeneca strongly bought into this opportunity," says Al Dossetter, founder and managing director of MedChemica. "AstraZeneca has been joined by Roche/Genentech, and the database contains around 1.2 million data points so far. However, the more data there is to mine, the better the results will be."

The consortium is open to other large biopharma companies, and discussions are ongoing. As a consortium, all partners have a say and can suggest where additional data could improve the dataset overall, even agreeing to share costs where further testing would be advantageous or match the addition of equivalent amounts of data. There will be no "reach-through" claims or tiebacks for any molecules generated as a result of the collaboration. "More companies will create bigger databases and, therefore, better rules. This should be synergistic rather than additive," says Boehm.

There will also be opportunities for collaborations with academia. The benefits of these will be two-way — for both the academic researchers and the science behind the database. "We plan to have an online tool available by the end of 2013. This could give academia and small companies access to the technology on a pay-as-you-go basis. This would support research and provide us with another revenue stream," says Dossetter.

> "We remove identifiers to protect privacy and store data in a private cloud to ensure it is secure."
>
> Saeid Akhtari, cofounder, president, and CEO, NextBio

As with all precompetitive collaborations, security is an important issue. However, Boehm is reassuring, saying, "The beauty of the collaboration is that the data is extracted and analyzed in such a way that we share the rules but not the structures of the molecules. Many companies are recognizing the advantages of precompetitive collaborations, and I expect to see more in the future. I look forward to seeing what comes out of this collaboration. It could be a big step in drug development."

NextBio has created a database with billions of data points from a range of different types of information, such as genomic, proteomic and metabolomic data, molecular profiles, and clinical trial results from public and private databases, as well as clinical data from individual patients. The company analyzes the data using its proprietary algorithms.

"One of the drivers for the advances in Big Data in healthcare research is the improved efficiency in producing molecular profiles, as sequencing costs are falling," says Saeid Akhtari, cofounder, president, and CEO of NextBio. "Each patient whose data is added to the system makes it smarter."

CUTTING THROUGH THE ROCK FACE: THE BIG DATA CHALLENGES

Data mining and Big Data bring with them many challenges. One of the biggest challenges in data mining is the consistency of the data, which can come from many sources. However, as Akhtari explains, this is important since it reduces the risk of false positives and is the point where a human touch can be essential to provide quality control. "There are many data repositories worldwide containing a lot of heterogeneous data. This data has to be standardized and indexed to be searchable, and results from queries need to be returned in real time via an intuitive interface to enable scientists to continue their research," Akhtari adds.

As Boehm explains, this isn't always as easy as it looks: "There have been some interesting papers on how to analyze Big Data, but when you look closely, you realize it takes a huge amount of curation and isn't necessarily scalable. What's possible on a thousand records won't necessarily work on millions. What's needed is a way to build compatible and well-annotated databases and analyze the databases using processes that can be scaled up."

Textual information makes up the bulk of the information generated by the biopharma industry, and one of the exciting possibilities for data mining would be to be able to link this with the other available information and analyze it. However, as Gardner explains, this has its own issues. "Analyzing text is challenging because so many meanings of words are changed by their context. You can't assume that two people using the same word will necessarily mean the same thing. It will be necessary to resolve issues at a very detailed level."

It is also important to know the data well, as this will influence how it is searched and analyzed and the quality of the outputs. Understanding the data also has an impact on the questions asked of the data. "For example, do you know the context in which the data was discovered? Have patients been diagnosed using a specific methodology or were they self-diagnosed? Were they given the same treatment protocol or even the same dose? Were the endpoints the same?" asks Gardner.

Another key challenge is data security. This is important both for patients and drug developers. "Data security and patient privacy is critical. We remove identifiers to protect privacy and store data in a private cloud to ensure it is secure and to provide confidence for our clients," says Akhtari.

THE FUTURE OF BIG DATA AND DATA MINING: THE ROUTE TO THE MOTHER LODE

If these challenges can be resolved and large sets of data (e.g. drug information, FDA-approval documentation, patents) can be combined successfully, then the future of Big Data and data mining could be very exciting. "The future of data mining, we believe, is in making data available to the community and connecting stakeholders," says Akhtari.

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Guidelines For Launching A Successful Biotech Company

By James Smith, Ph.D.

Every young start-up wants to make the next blockbuster product. We analyze the market, identify a huge patient population with an unmet need, and attempt to create a product that will meet that need. It sounds feasible at first glance; after all, what better way to get a return for investors than to deliver a product with a huge, sustainable customer base that has no other alternatives for treatment?

Of course, this is easier said than done. Such a grandiose endeavor comes with a tremendous development cost and often a very high regulatory bar. The drug development process is inefficient, almost seemingly by design, tolerating countless dead-end iterations during the molecule discovery phase. And the larger the market, the larger the clinical trial burden will be, with ever growing numbers to reach statistical significance, particularly if the product only has a modest clinical benefit.

While this paradigm may have worked in the past for established pharma companies with deep pockets and vast research and development infrastructures, it is a recipe for disaster for a budding start-up. Time and again, young companies fall into the unfortunate trap of overextending scarce resources to develop a product for a huge market, not realizing the unrealistic burden that they have undertaken, and ultimately running out of funding before they can finish what they started.

There are various ways that entrepreneurs can improve their chances of success. The successful start-up will have a well-defined commercialization strategy that is efficient and flexible, balancing commercialization progress with innovation, and leveraging partnerships and collaborations with industry experts. With funding most commonly being so tight during product development, an efficient commercialization strategy can prove to be the difference between failure and completing the only goal that really matters: crossing the line of market approval and introducing the product to the public.

DESIGN AN EFFICIENT AND FLEXIBLE DEVELOPMENT PLAN

As desirable as it sounds, a single, straight path to market simply does not exist. Inevitably, companies will encounter challenges and roadblocks that will delay progress. The setbacks could be seemingly endless: finding the right drug profile during discovery may not happen quickly, lead candidate prospects may have unfavorable safety profiles, or the product may have other undesirable characteristics or not be stable enough to meet expected requirements. However, you can mitigate these risks through careful comprehensive planning in which multiple possible pathways to market — with their own relative risks and benefits — are mapped out and evaluated in advance. This "guided flexibility" approach allows a company to maintain a development strategy that remains efficient in the face of obstacles while capitalizing on new opportunities as they present themselves.

NanoSmart Pharmaceuticals, Inc. for example, has employed a highly flexible commercialization strategy as it takes on the challenge of developing a tumor-targeting drug delivery platform. The plan to achieve regulatory approval of the platform is to reformulate an existing FDA-approved drug by enclosing it within the antibody-targeted lipid nanoparticle. NanoSmart considered various APIs with which to commercialize its platform and began formulation efforts. When the first formulation candidate presented unacceptable stability issues that were found to be inherent to the API, the company was able to continue development of the platform by elevating the priority of other APIs that exhibited more favorable biochemistry. Due to the initial design of the project and adequate contingency planning, the unanticipated flaws of the API have not substantially delayed development of the platform.

FIND A COST-EFFECTIVE REGULATORY PATH

The regulatory path of a drug product has critical relevance in the clinical phase of development, as it directly affects the most costly aspect of commercialization: clinical trial size and length. For example, per capita Phase 3 clinical trial costs exceeded $40,000 in 2011, a staggering 70 percent increase from 2008 (Cutting Edge Information, 2011). Careful clinical trial planning is therefore crucial to the survival of the company.

Perhaps the best option to leverage existing regulatory pathways is the orphan-drug pathway. Orphan indications — rare diseases that have very small patient popu-

lations with unmet medical needs — offer substantial financial incentives such as tax benefits and additional patent protection. But more importantly, the orphan pathway allows companies to tap into rapidly growing support networks that increase a company's chance of success.

Because products developed for orphan indications benefit a patient population that has no other treatment alternatives, the FDA has been historically flexible in evaluating efficacy, allowing data collected from smaller and/or shorter trials and allowing expedited review. In fact, a 2011 study performed by NORD (National Organization for Rare Disorders) found that 66 percent of approved noncancer orphan drugs between 1983 and 2010 received FDA approval with flexible evaluation criteria. This is an attractive incentive that could reduce a product's time-to-market. With few exceptions, the FDA has reviewed and approved orphan drugs much more quickly than non-orphan drugs (Figure 1).

The orphan-drug pathway can be strategically used to accelerate a company's time-to-market while decreasing the overall commercialization cost both before and after FDA approval. Revenues can then be used to pursue further clinical trials to expand the drug's indications for use with additional orphan or non-orphan indications.

Similarly, NanoSmart plans to commercialize its drug delivery platform by achieving its initial approval with a reformulation of an FDA-approved drug already approved for an existing orphan indication, such as a rare pediatric cancer. The initial approval will validate the platform's potential to improve therapies, thereby mitigating the regulatory burden of future orphan and non-orphan filings, and facilitating licensing agreements with other pharmaceutical companies looking to extend patent life.

BALANCE PROGRESS VS. INNOVATION

For a start-up, much of its true value lies in its intellectual property, not just the size of its potential customer base. While constant, measurable progress toward defined goals is a key element that drives investments, start-ups should also be concerned with simultaneously enhancing their valuation. Therefore, whenever practical, a company should focus on developing an IP portfolio that will facilitate additional regulatory approvals, increase future revenue potential, and extend the company's potential beyond the life cycle of any single product. Importantly, broad intellectual property also mitigates the investor's risk of any single failure or substantial challenge to product development. Focus on the prod-

uct pipeline and continuous discovery efforts are, therefore, hallmarks of success for both start-up and established large pharma companies.

An example of this is NanoSmart's IP expansion in the face of development challenges. NanoSmart initiated operations with a platform technology when the initial discovery phase of its targeting antibody was complete. The company is now working to use the targeted delivery system to reformulate various cancer drugs. In order to accommodate a larger array of APIs with different biochemical properties, the company innovated a novel approach to the delivery mechanism. The lessons learned from formulation challenges resulted in the expansion of the company's intellectual property portfolio with a second platform technology, which opened up additional paths to commercialization and increased prospects for collaborative or licensing opportunities.

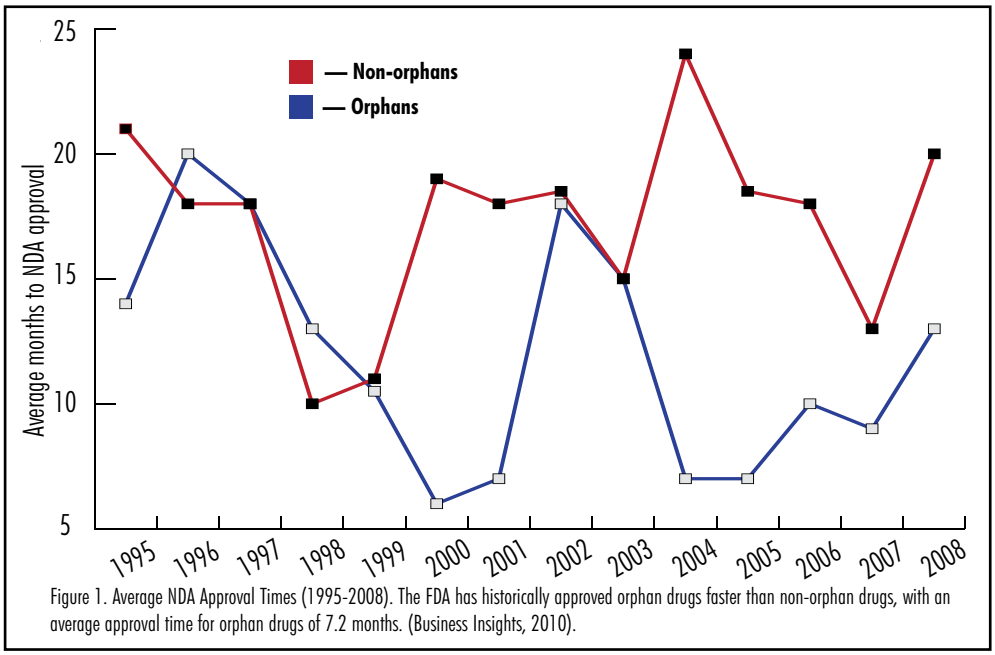

Figure 1. Average NDA Approval Times (1995-2008). The FDA has historically approved orphan drugs faster than non-orphan drugs, with an average approval time for orphan drugs of 7.2 months. (Business Insights, 2010).

LEVERAGE PARTNERSHIPS

The lesson learned from countless other companies that successfully crossed the line of market approval is that development and commercialization goals are most attainable when there is a network of trustworthy, proven experts supporting the project. Generally, it is much more difficult to cultivate all the necessary expertise in-house, and so the industry is witnessing a shift toward external partnerships and collaborations. In fact, much of the industry's focus over the past 10 years has been on developing the infrastructure, capabilities, and regulatory frameworks through external consortiums and innovation incubators. Such developments mean that new start-up companies have resources and support options that were not previously available. The collaborative environment between industry, government agencies, and academia is rapidly growing and establishing new paradigms for interactive product development. This very exciting trend is precisely why innovator companies are being increasingly seen as potential engines for advancing future pharmaceutical drug development.

A SHIFT TOWARD RARE DISEASES

The pharmaceutical industry as a whole is seeing an increasing focus on rare diseases. In recent years, personalized medicine has dominated much of the industry's focus for both large and small pharma. In fact, the proportion of all drug approvals that receive orphan indications has been steadily increasing over the past 15 years. Large companies like Novartis, Roche, and Genentech have used the orphan pathway to efficiently expand their pipelines and grow their markets.

In conclusion, product development in a start-up setting is never easy, and only a fraction of companies that attempt to commercialize their novel technologies is able to accomplish that goal. As daunting as the obstacles may be, now more than ever, the tools, resources, and industry infrastructure exist to support and guide start-up operations through the very challenging process of product development and commercialization.

In order to succeed, start-ups must be able to advance effectively and efficiently on limited funding as well as mitigate the risks inherent to the development process as much as possible. In this way, companies can maximize the potential for successful product development and give their supporters the return on investment they deserve. With the right commercialization strategy, it is possible to cross the line of market approval with a fraction of the funding that was once believed necessary.

About the Author

James Smith, Ph.D., is president of NanoSmart Pharmaceuticals, Inc. He has over 15 years of experience in regulatory affairs and the development of novel technologies from concept through commercialization. Dr. Smith obtained his Ph.D. in pharmacology and toxicology from the University of California, Irvine.

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What Drives Innovation Today?

Roger Hayes, Ph.D.

Hayes is VP and GM of laboratory sciences at MPI Research. For nearly two decades, he has led strategic and research initiatives for large pharmaceutical companies that included both GLP and non-GLP preclinical studies as well as clinical trials.

Change in the biopharmaceutical industry is the new norm prompted by several notable patent expiries of billion-dollar blockbusters. In the United States alone, there were 13 companies that from 2008 to 2012 each saw over $5 billion in revenue lost because of patent expiration of their major products. In response, Big Pharma companies have consolidated (e.g. Merck/Schering Plough, Pfizer/Wyeth, Roche/Genentech) and focused their efforts on shoring up their late-stage pipelines, often through in-licensing or marketing collaborations with biotech and other niche companies.

The Affordable Care Act has medical reimbursement payers increasing their scrutiny of what drugs make it onto formulary lists; incremental improvements in efficacy are not enough. Consequently, during these tough economic times, the biopharmaceutical industry must take a more thoughtful approach to drug development that maximizes return on investment rather than the more speculative high-risk/high-reward strategies of the past. Drug candidates can no longer be just "me-too" copies.

Developing new types of drug candidates requires innovative study designs that on the one hand must be highly customized but on the other still cost-effective — even commodity-priced. This is particularly true in the preclinical development space. The challenge now lies in finding new ways to stay innovative while bringing new drugs to market.

THE DIFFERENT DEGREES OF PARTNERING

The FDA is encouraging innovative drug development by introducing the concept of "breakthrough" drug status that offers a collaborative approach to speed such drugs to the market faster. To be competitive, biopharmaceutical companies need to implement more efficient processes that reduce their R&D budgets while simultaneously increasing the productivity of their R&D groups. It would appear that our industry has begun to respond because more new molecular entities (NMEs) were approved in the United States in 2012 than in any year since 1999.

To sustain this pace, the industry has turned to a variety of partnering opportunities, with biopharmaceutical companies frequently seeking partners that are willing to share the rewards and risks of drug development. Core functions once kept in-house are now being performed through collaborations with academic research organizations, specialty biotech companies, and CROs.

For example, the outsourcing of preclinical safety assessment studies is a common practice. However, the increased demands of today's drug development environment require that toxicology studies incorporate molecular biomarkers, imaging, and companion diagnostics to provide better safety profiles for drug candidates. One innovative modality is molecular imaging (MI), which provides investigators with an early-stage solution to assess exposure at the target site, binding to the target of interest and expression of the desired pharmacology.

Indeed, some companies have almost entirely outsourced their drug discovery operations, replacing internal lab capacity with partnerships throughout the world. Others outsource selected steps in the drug discovery process such as hit confirmation, lead generation, lead optimization, and/or exploratory safety studies.

PARTNERING TO SPUR INNOVATION

The partnering model is all about creating efficiency — allowing a biopharmaceutical company to continue to innovate and evolve its science while operating more efficiently than its competitors. Likewise, any outsourcing partner needs to be an extension of the sponsor's internal team and, as such, be innovators in their own right. In fact, outsourcing partners are becoming fertile grounds for innovation. The application of knowledge gained from dealing with a diverse array of sponsors and their programs offers unrivaled opportunities for creative thinking on a new program. While biopharmaceutical companies might be dealing with one or two chemical scaffolds for a specific therapeutic area, an outsourcing partner might have to deal with hundreds of unique molecular entities in a year.

As the biopharmaceutical industry continues to evolve, the need to maximize the value of internal operations and free up R&D dollars is paramount to fostering innovation. To stay successful, companies are being forced to reevaluate what services/programs they need to maintain in-house, and for those that don't make the cut, the solution will continue to be enlisting the help of outsourcing partners such as academic research organizations, specialty biotech companies, and CROs — and challenging them to be the engines of innovation.

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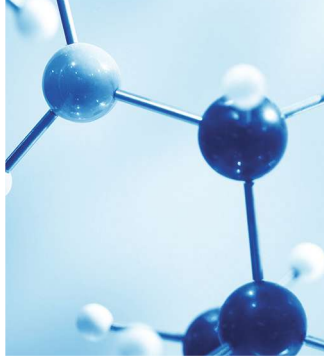

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How To Apply QbD Principles In Clinical Trials

Frederic L. "Rick" Sax, M.D.

A former academic cardiologist, Dr. Sax is global head for the Center for Integrated Drug Development at Quintiles. He leads the design of solutions to enhance the quality of program and trial design while driving efficiencies in cost, time, and process.

The biopharmaceutical manufacturing industry has used quality by design (QbD) principles for decades. The essence of QbD is designing with the end in mind (in this case, the efficient manufacture of a high-quality drug product). This approach emphasizes that the operative word in QbD is not quality, but design.

Conventional batch biopharmaceutical manufacturing was very inefficient. A given step of the overall process was completed and then samples taken for quality testing. Production was therefore halted until the results of the quality testing became known, meaning personnel and expensive machinery sat idle until then. In a multiphase process, this led to constant sampling and constant waiting to be given the go-ahead, assuming the results were positive. Negative results led to an even worse scenario in which a batch of intermediate product had to be reprocessed or even discarded. In both scenarios, neither time nor resources were used efficiently.

A much more efficient approach is to design quality into the manufacturing process. Employment of automation and continuous process monitoring allows product attributes to be measured in real time and therefore facilitates adjustment of operating parameters via feedback/feed-forward controls during the manufacturing phases. This strategy substantially reduces the need for reworks.

Given the demonstrated success of QbD in manufacturing, it is both paradoxical and unfortunate that it has not yet become an integral component of biopharmaceutical R&D and clinical trials — incorporating QbD is one of the few levers that the biopharmaceutical industry can pull to increase its probability of success. The reason QbD principles have not transferred to R&D is that clinical trials are expert-driven rather than process-driven. However, the key aspects of these two operational modes are not mutually exclusive: Within a structured process that facilitates efficient decision making, there is still room for expert input and creativity.

QBD ELEMENTS: PLAN-DO-CHECK-ACT

The "Plan-Do-Check-Act" framework succinctly encapsulates the key elements of QbD. The "Plan" phase requires "design diligence." The study design presented in the protocol must focus on proactive quality risk management and, specifically, scientific risk assessments: ensuring the safety of the study participants who will be recruited via carefully determined inclusion and exclusion criteria, the study's scientific objectives, and the assessments and procedures that will generate the data collected. Operational risk assessments focus on feasibility considerations (e.g. can appropriate and sufficient investigational sites be secured) and operational risk (e.g. supply chain issues, procedures such as imaging, patient-reported outcomes, lab assays, data integrity). Operational plans will be created for site/country selection, quality, data monitoring, and safety.

In the "Do" phase of the cycle, training investigational sites, principal investigators, monitors, and clinical trial educators is the first step. Then you need to set up the process for overseeing trial execution, including prospective alerts, triggers, and risk mitigation plans that deliver against iterative project management plans.

As you execute your trial, the "Check" phase employs sophisticated reporting software housed in a central data-operations center to provide near-real-time access to blinded data at the participant level. This enables visualizations of core study indicators such as enrollment site, site performance, and monitoring performance. Dashboards displaying expected versus actual enrollment, for example, are potent tools that provide detailed information in a readily assimilated manner. Alerts can also be programmed to indicate unacceptable values for multiple indicators, including safety concerns and endpoint accrual. Data cleaning status is also monitored and the quality assurance database assembled.

The "Act" phase entails the final proactive (rather than reactive) step in QbD. It involves preemptive project management and proactive risk mitigation using the information gleaned from the "Check" phase. Reforecasting is conducted based on information gained to date and QA/quality management processes followed.

In conclusion, the success of QbD in the manufacturing side of the biopharmaceutical industry should be a powerful motivator for those on the R&D side to embrace it, too.

Preventing Culture Clash In The Changing Healthcare Landscape

Pat Cormier

Increasingly, Big Pharma is partnering with smaller drug developers to create new, innovative products to keep their portfolios relevant, pipelines full, and themselves from falling behind. We are even seeing the once unimaginable — rival large players, such as Merck and Pfizer, partnering on a new generation of diabetes drugs. In theory, these partnerships are beneficial to the large companies because they allow them to stay competitive by bypassing or sharing the often arduous R&D stage and are good for the small developers because they are able to bring their pioneering products to market more quickly, without the time and expense of building infrastructure. Unfortunately, these unions often end up being far from harmonious.

The problem? Culture clash

Two organizations that vary so greatly in both size and structure rarely operate in similar ways. The small drug developers are nimble, used to moving rapidly and with a singular focus — innovation. Meanwhile, the big pharmaceutical companies are slowed down by bureaucracy and ingrained processes.

Culture clash can ruin these partnerships, leaving both parties in an undesirable situation. Although it may seem like an incredibly complex issue, there are a few simple things that leaders can do to avoid what starts as a "win-win" from becoming a "What were we thinking?"

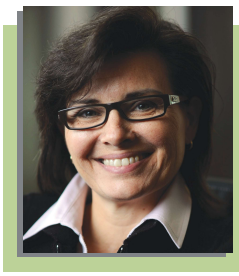
Discuss your goals beforehand. Before the handshake is forgotten and the ink dries, agree on what opportunities you both are trying to take advantage of and capitalize on. This type of frank conversation can uncover incompatible priorities or competing objectives. Once the deal is done, this shared vision can be used as a focal point to build urgency necessary to overcome future barriers.

Remember why you partnered in the first place. It's essential to keep in mind the reason the partnership exists at all — your partner has something you need. You have opted for speed over building it yourself, whether it be drug- or infrastructure-related, so it's important to acknowledge this and respect what each of you brings to the table — and not just among leadership, but throughout both organizations.

Separate but equal seldom works. Often, neither side views the other as equal (think compensation plans, reporting systems, etc.), which creates an us-versus-them mentality. Look for ways to align and integrate when and wherever possible.

Don't let egos get in the way. As much as we would like to deny it, egos can play a major role in culture clash with "they-need-us" attitudes. Remember, you are each successful in the area the other covets.

It really boils down to one thing: It's not all about you. As long as you view your partner with respect and as working with you, not for you, you'll sidestep many of the problems associated with culture clash and be on your way to a fruitful partnership.



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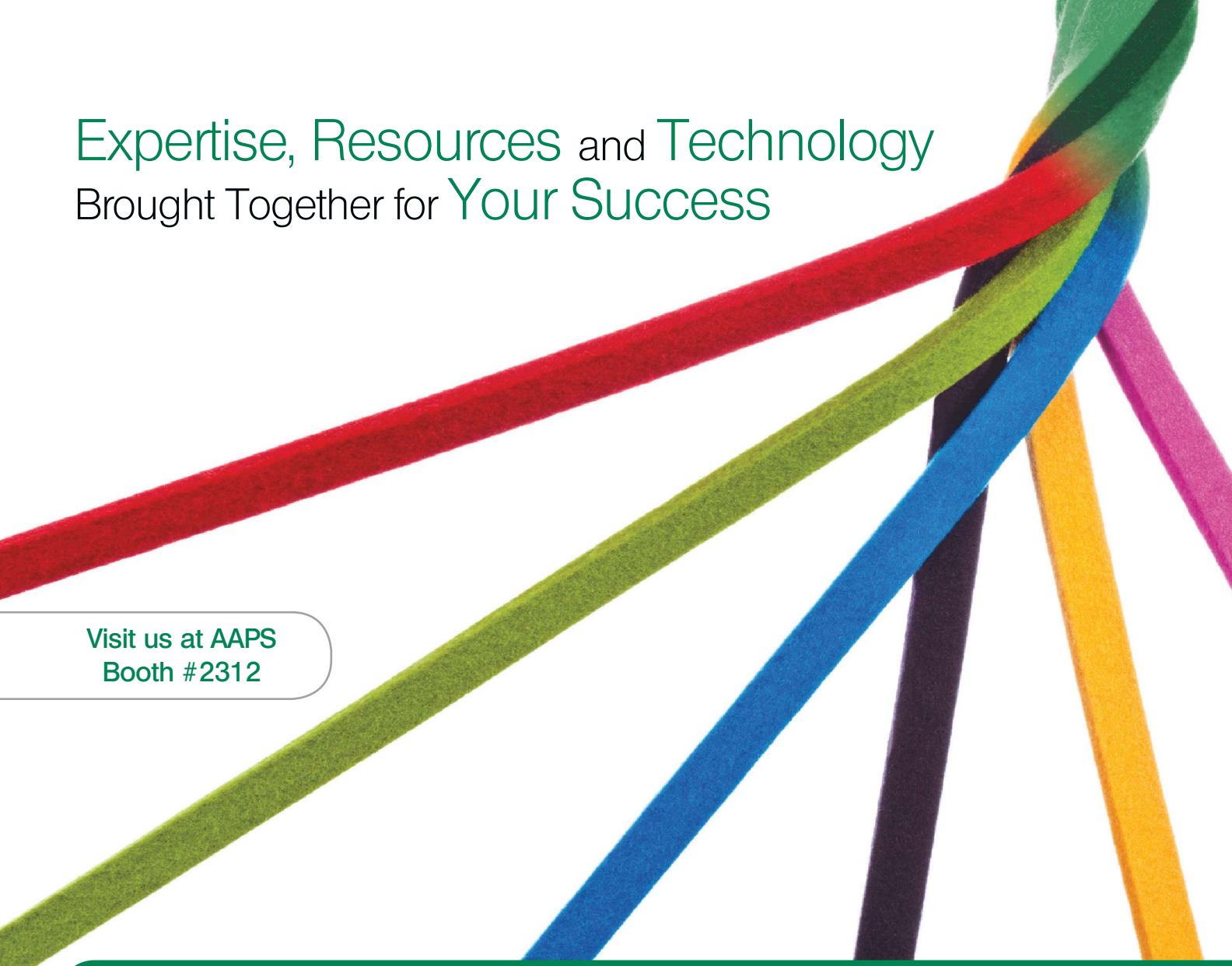

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