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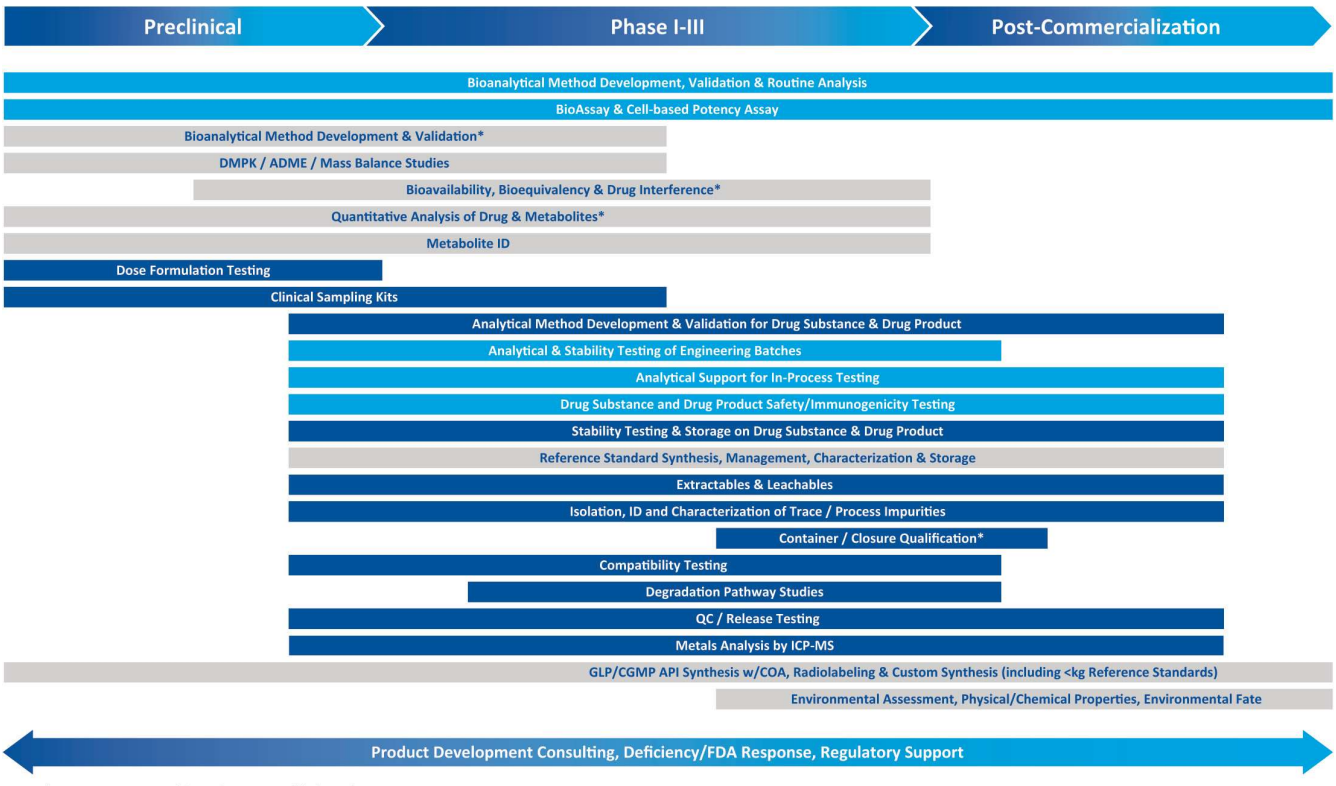

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Bayer AG Shows How To Foster Big Pharma Innovation

Board of management member **Kemal Malik** explains why 70% of his time is devoted to innovation and what that term really means at Bayer AG. **p. 24**

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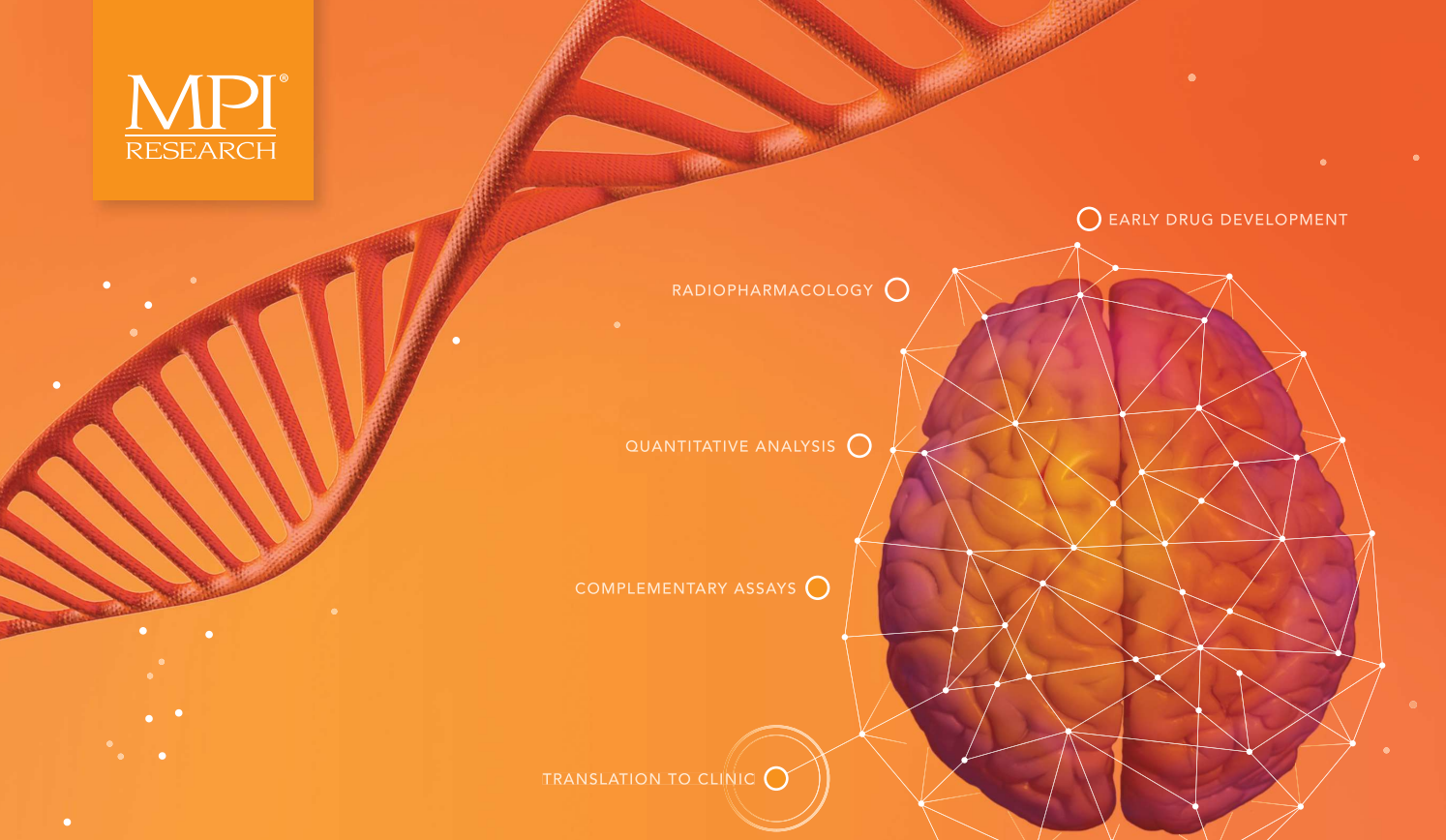

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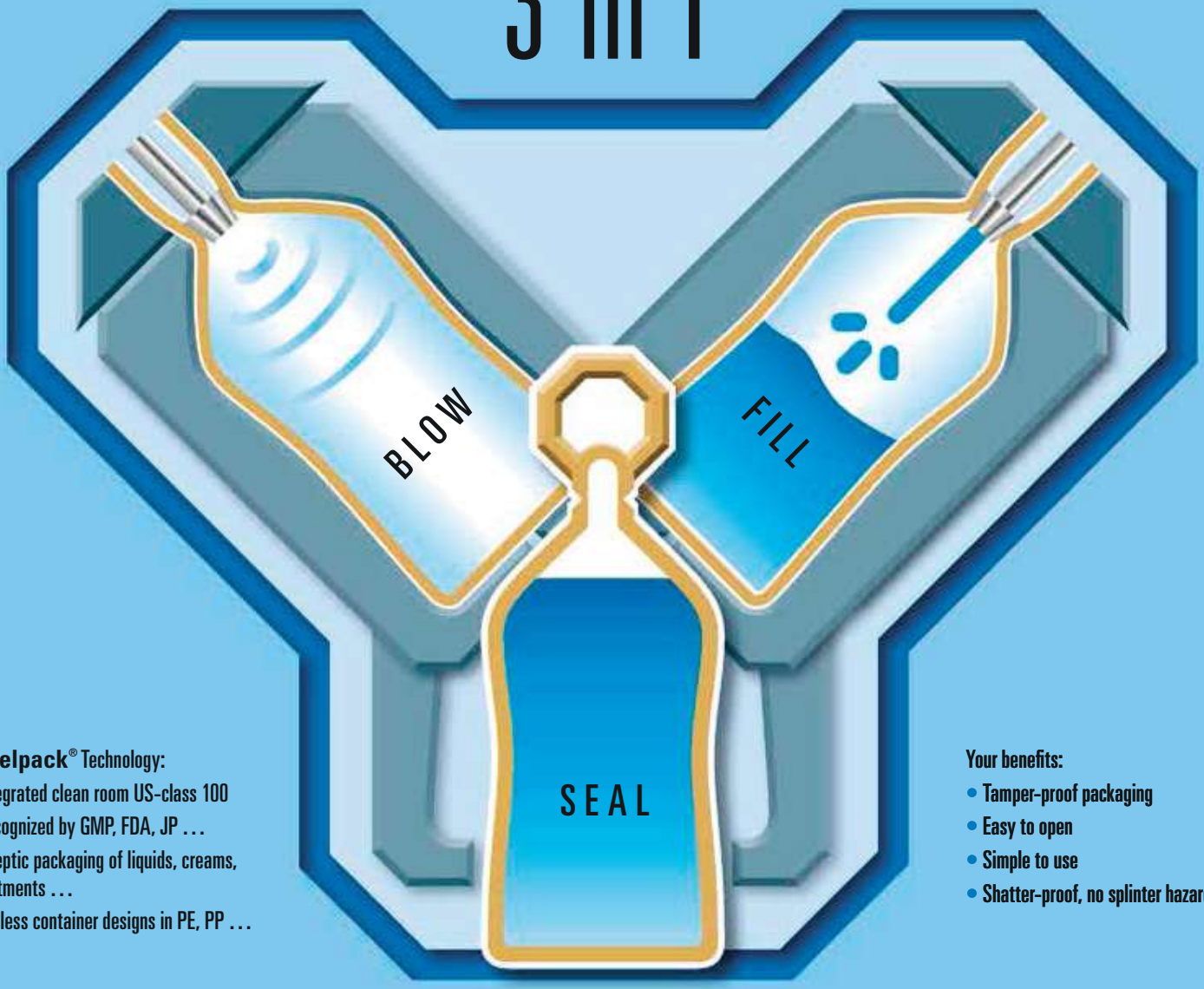

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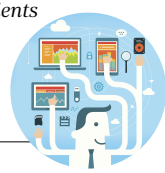

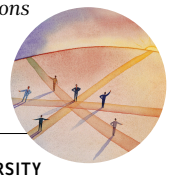

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What Is The Biggest Challenge To Innovation In BioPharma?

ROB WRIGHT Chief Editor

Toward the end of my conversation with this month's cover feature subject, Bayer AG board of management member and global innovation leader, Kemal Malik, I inquired if there was a question he hoped I had asked. "I guess I thought you'd ask me, 'What is the biggest challenge to innovation in the life sciences,'" he replies. Elaborating, Malik continued, "Society needs to understand the value of innovation, its importance, that it comes at a price, and that innovation doesn't happen for free." For example, the cost of bringing the anti-coagulant, Xarelto, to market for Bayer and its collaborative partner, Johnson & Johnson cost > $2 billion.

Now truthfully, I have heard this message before, often while attending PhRMA's annual meeting. However, what surprised me is Malik's next comment. He contends society's failure to understand that life sciences companies need a reasonable return is the fault of life science leaders — not society. "As an industry, it is the responsibility of senior leaders to communicate, educate, and engage with stakeholders when criticism is levied by NGOs [non-governmental organizations (e.g., non-profits, patient advocacy groups)]. We [senior leaders] have been unwilling to do that." In addition, Malik said, "We can't rely on industry trade groups and associations to go out there and do it for us."

At this point in our conversation I shared with Malik a short story of a recent engagement I had with a member of an NGO which, coincidentally, involves one of Bayer's products. While attending the 33rd Annual J.P. Morgan Healthcare Conference, Amanda Rusmisell (@A3Rusmisell) was tweeting about an upcoming rally against Essure, Bayer's nonsurgical birth control product. As she included the conference twitter hashtag, #JPM15, I noticed the tweet and inquired about a time and location for the rally. Having previously worked for Organon Pharmaceuticals, which had developed a wide range of contraceptive products, I was curious and more than willing to engage. But immediately after tweeting that she would let me know the details of the rally, Rusmisell followed with the tweet, "@Rfwrightlsl Looks like your magazine is in the business of helping businesses to get things to consumers faster. That isn't always good." Considering the negative social media firestorms that have engulfed companies (e.g., Chimerix) that have decided not to sooner provide drugs still under investigation to patients, I was surprised and replied, "Really? Tell that to a cancer patient." Though perhaps not her intent, Rusmisell exposed one of the challenges with social media — space limitations impeding effective communication. She may have intended to send a playful jab, but it was perceived as an attack.

I asked Malik how he goes about engaging with combative stakeholders. "Very actively," he responded. Regarding Essure in the United States, he affirms, "We have said of the social media forum, 'Come and talk to us,' we have an open invitation to all of those people, and will engage with people as individuals or groups, and will do so at the physician level."

Though we often view society's misunderstanding of the value our industry brings to mankind as being a problem, perhaps the real problem resides elsewhere and requires a mirror. Leaders aren't victims, and there is only one person who can stop them from being positioned as such.

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Q What top trend should pharma executives be taking a more proactive approach to?

A REIMBURSEMENT IS THE HOT TOPIC. The U.S. remains sheltered relative to the EU and other locations, but this is changing rapidly, and the industry is inadequately prepared. Witness the thunderclap that hit the markets at the end of 2014 when Express Scripts announced it would exclusively offer AbbVie's HCV (hepatitis C virus) treatment and not cover Gilead's. CVS Health promptly countered, offering preferred status to Gilead drugs. Prior to that, another drug made headlines when Sloan Kettering physicians published an op-ed in the *NY Times* saying they would not prescribe a new cancer drug that was similar to another but priced twice as high. It's no longer only an issue of achieving favorable "tiering" on reimbursement formularies. Where competition exists, companies will increasingly struggle to get on formulary and be required to make compelling value cases for their products.

RON COHEN, M.D.
Ron Cohen, M.D. 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 are the keys to running a successful business in the midst of immense distraction (e.g., hostile takeover)?

A TREAT AND RESPECT THE STAFF as professionals, be honest about the situation, and provide as much information as possible. In this age of Twitter, online message boards, Instagram, news feeds, etc., information is out there – correct or fabricated – for all to see. Executives need to react and do damage control in a transparent and honest way before things get out of hand. Another way to manage morale for maximum productivity is to enlist trusted leaders and have them communicate frequently with key staff. Often, being productive, in addition to keeping the mind off of the distractions, will actually help with the negative situation and position the organization to come through this troubled time in a positive manner.

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

Q What macro trend have you noticed beginning to impact the way you do business?

A AS A LONG-TIME HILL STAFFER AND GENERAL COUNSEL for an advocacy organization, I have seen executives interact with members of Congress and senior federal officials from both sides of the table. When these meetings don't go well, it's usually because the advocates do not adequately know their audience. You can't assume a busy member of Congress or agency official will know or care about your issue in isolation. You must provide context that matches the official's interests and responsibilities. Within the first five minutes, everyone in the meeting should know why they are together and why that makes sense based on their respective roles and the issues under discussion. By the end, everyone should know what the specific "ask" is. Clarity in these areas demonstrates respect for the officials' time and position, and not only leads to effective and efficient meetings but also usually return invitations.

MARY ROSE KELLER
Mary Rose Keller, VP clinical operations at Tocagen, has 30+ years of industry experience in clinical development strategy and execution of global Phase 1 to 4 clinical trials for drug, biologic, and diagnostic products.

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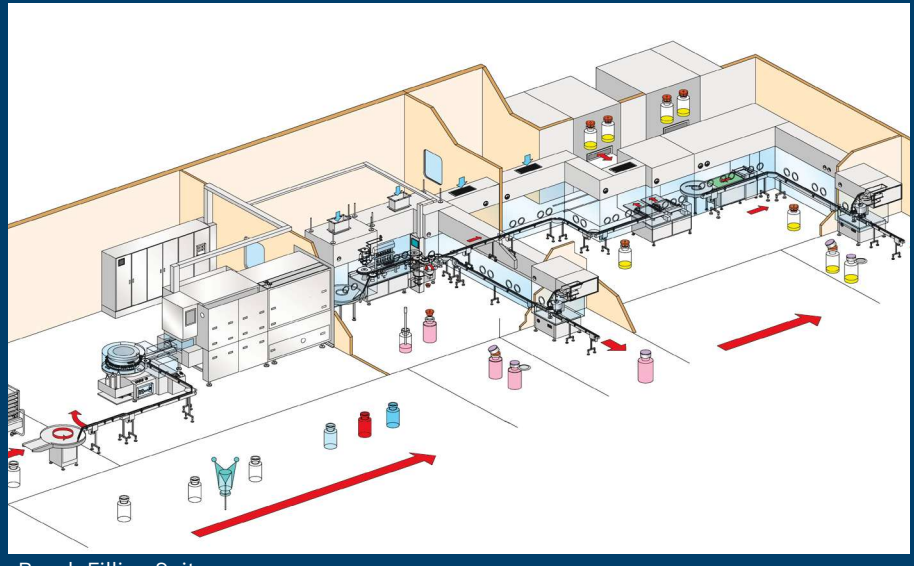

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Pending Supreme Court Decision On Obamacare Requires Solutions

JOHN McMANUS The McManus Group

"When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean—neither more nor less." "The question is," said Alice, "whether you can make words mean so many different things." "The question is," said Humpty Dumpty, "which is to be master—that's all."

–LEWIS CARROLL

Last month the Supreme Court heard oral arguments for King v. Burwell on whether subsidies to health insurance policies offered through the federal exchange (covering individuals in 34 states) are legal, since the statute explicitly reads that subsidies may only flow through exchanges "established by a State." The court is expected to render its verdict in June, and it is anyone's guess how it will rule.

What is the Obama administration's backup plan if the 87 percent of the 7.7 million people enrolled in the federal exchange lose their premium subsidies? Answer: the administration has said there is no plan.

In congressional hearing after hearing, the administration has refused to say whether it has any contingency plan at all. The following exchange between Senator John Cornyn (R-TX) and Health and Human Services Secretary Sylvia Burwell was typical:

Cornyn: "So let me ask you again: If the Administration loses in the King vs. Burwell case, do you believe you already have the authority to make an administrative fix? Or will you come to Congress and ask for additional legislation?"

Burwell: "Senator, I am focused right now on implementation."

Cornyn: "Mr. Chairman, these hearings are absolutely no use to us if the witnesses refuse to answer straightforward questions, which this witness has repeatedly done."

At a House hearing, Energy and Commerce Subcommittee Chairman Joe Pitts (R-PA) asserted HHS officials had drafted a 100-page document on potential actions the agency could take if the Court strikes down the subsidies. Burwell responded she was aware of no such 100-page document. Perhaps the document was 99 pages?

The Administration must believe that admitting it has a contingency plan to assist those who would lose subsidies under a straightforward reading of the law would reduce pressure on the court to preserve the ACA. The Administration is arguing — beyond any credulity — that it has no contingency plan to a negative ruling in King v. Burwell and that such a verdict by the court would result in a healthcare apocalypse that is beyond repair. Therefore, the ACA must be upheld because it is doing so much good that the law Congress actually passed should be disregarded by the court in lieu of the law they wish Congress had enacted.

In that same vein, dozens of powerful health lobbies have submitted amicus

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briefs arguing that the court should focus on the result of its decision, not the legislative language of the statute. Was it hyperbole when the hospital lobby's brief stated, "This is no abstract case about principles of statutory construction; petitioners' position, if accepted, means more people get sick, go bankrupt or die"? That same brief claimed it would be unfair for hospitals to accept substantial Medicare cuts but lose their new subsidized customers.

Justice Antonin Scalia dismissed this rationale in oral arguments, suggesting that "If there are disastrous consequences, Congress will react."

Indeed the Republican chairmen of the committees of jurisdiction have outlined a plan to provide an "off-ramp" to Obamacare should King v. Burwell declare the subsidies illegal. The plan would retain subsidies, perhaps for a limited period of time, and permit increased flexibility for individuals to enroll in health plans that better fit their needs, instead of the current plans which must comply with munificent benefit mandates that drive up costs. But reinstating subsidies obviously requires a Republican Congress to spend money in this area, which could be construed as tacit endorsement of a program they've been fixated on repealing. Enacting that plan will be a difficult task but a political necessity, as no family should pay for a political party's overreach.

Yet the plan is certainly superior to the Obama administration's mantra that it has no backup plan of any kind!

Of course, an alternative to congressional action would be a state response to the issue — allow states to establish their own exchanges, as originally conceived in the legislation. This option was suggested by Justice Samuel Alito during the oral arguments.

However, that raises a similar constitutional question that blindsided many in the health policy community when the Supreme Court last ruled on Obamacare in 2012: undue coercion of states by the federal government. In its decisive 7-2 decision, the court held that conditioning federal subsidies for currently covered Medicaid beneficiaries to only those states that expanded Medicaid to cover other indigent populations was "overly coercive to the states," even though the federal government was picking up between 90 and 100 percent of the tab. This decision emboldened nearly half the states — mostly controlled by Republicans in the South and Mountain West — to refuse to undertake Medicaid expansions. Many poor people in those states still have no coverage because the statute explicitly prohibits insurance exchanges from subsidizing anyone with income below the poverty level.

It is notable that Justice Anthony Kennedy wondered in oral arguments about the "dynamics of federalism." Kennedy stated, "If your argument is accepted, the states were told to establish exchanges in order to receive money (for their citizens) or send the insurance into a death spiral; isn't that coercion?"

If Kennedy joins the liberal coalition protecting Obamacare on the state coercion basis, it will not matter if the Chief Justice holds that the subsidies in the federal exchange are illegal. The law would remain intact.

Upholding the clear language of the law and declaring illegal the subsidies through the federal exchange would make for a tumultuous and active 114th Congress in healthcare. Congressional inaction will not be an acceptable outcome for either party. Divided government may actually work to their benefit as each party must take ownership over a solution that solves the problem. Could that solution be a Democratic priority of subsidies for low- and middle-income individuals combined with Republican priority of greater flexibility and more affordable options?

> *"Wouldn't it have just been easier if the legislative language in Obamacare articulated what its proponents say it* really *means?"*

Maybe. But the time to enact such legislation is short, and the dynamics are not good as we roll into the fall and the next presidential election approaches. A half dozen senators wake up in the morning and see a potential president looking in the mirror, and they may prefer scoring political points with their bases to making the tough compromises necessary to enacting bipartisan legislation.

Wouldn't it have just been easier if the legislative language in Obamacare articulated what its proponents say it really means? That would certainly reduce the level of mendacity that no Plan B is under consideration by the minions charged with protecting the president's signature domestic achievement. L

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

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SNAPSHOT

Resverlogix is developing a first-in-class selective BET (Bromodomain and ExtraTerminal Domain) inhibitor, RVX-208, as a treatment for atherosclerosis, plus other epigenetic BET inhibitors to treat or prevent critical health effects of cardiovascular disease, diabetes, and other widespread chronic diseases. It has announced positive data from three Phase 2 trials of the compound for several conditions, such as reduction in major adverse cardiac events (MACE) in diabetes mellitus patients, and is preparing to launch a Phase 3 trial this year in patients with low HDL, cardiovascular disease, and diabetes mellitus.

WHAT'S AT STAKE

The operative word is "epigenetic." Therein lies the key to a long-awaited goal in treatment of patients in disease areas harboring some of the largest unmet medical needs. The goal is discovery and development of therapeutics and preventatives with new mechanisms of action that mirror the latest knowledge of disease mechanisms. Resverlogix' epigenetic approach addresses genetically related disease states common to many conditions. BET-Bromodomain inhibition is an epigenetic mechanism that can turn disease-causing genes either on or off, returning them to a healthier state. The main expected benefits are reduced risk of major complications the diseases can cause.

"There are three forms of epigenetics — reading, writing, and erasing genes," explains Donald McCaffrey, president and chief executive officer. "Our small molecule binds to a gene reader, causing it to either up-regulate or down-regulate the gene." For example, RVX-208 binding to the reader appears to boost activity of the ApoA-I gene, causing production of ApoA-I and HDL proteins to rise. According to studies cited by McCaffrey, the MoA seems to translate into objective health benefits. "We have performed more than a dozen clinical trials in nearly a thousand patients, and in the last three trials in our Phase 2/2b program, we had a 50 to 55 percent reduction of events and a 77-percent reduction in patients with diabetes, according to a statistical analysis by an independent statistician," says McCaffrey. "The data was highly significant." In another, pooled analysis of two RVX-208 trials, the Cleveland Clinic found about a 70-percent reduction in subjects with an elevated C-reactive protein level.

In plans for the large Phase 3 trial, McCaffrey says, "Our aim is to prove the hypothesis that RVX-208 should be used on top of standard-of-care medicines in high-risk patient groups, so our focus is low-HDL diabetes — a huge untapped market. We hope to clearly articulate new data showing we can reduce MACE in those patients, creating a new, valuable weapon in the fight against diabetes."

Resverlogix will not cherry-pick the least ill patients or settle for proof solely by biomarker, as McCaffrey asserts has occurred with alirocumab, the PCSK9 inhibitor for hyperlipidemia from Sanofi/Regeneron. He says the company will enroll only high-risk atherosclerosis patients with low baseline HDL and diabetes mellitus. The MACE-reduction strategy reflects the serendipitous discovery of BET inhibition through positive health benefits noted in earlier investigations of the molecule as a simple ApoA-1 enhancer. Success with RVX-208 would fuel the company's further development of other BET inhibitors — all with the potential to shake up some long-neglected areas and free the industry from its prolonged fixation on niche products.

DON MCCAFFREY
President and CEO

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Latest Updates

March 2015:
Collaboration with Emerald Logic to identify drivers of drug response/efficacy in Phase 2 program.

November 2014:
Michael Sweeney, M.D., named Senior Vice President of Clinical Development.

September 2014:
RVX-208 leads to 77 percent relative risk reduction of MACE in patients with diabetes mellitus.

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Biopharmaceutical Outsourcing To CROs In Emerging Markets Surges For 2015

According to Nice Insight's 2015 pharmaceutical and biotechnology outsourcing survey, 63 percent of global sponsors outsource their drug research and development to global CROs in emerging markets, a remarkable 68 percent jump from the 2014 survey, when only 43 percent reported outsourcing to these markets. In addition, more sponsors (88 percent) today will consider working with a CRO in an emerging market, up from 84 percent in 2014.

NIGEL WALKER
Managing Director
at That's Nice

> *"As the trend to globalization of clinical trials continues, sponsors and their CROs seek new solutions to lower costs and improve trial efficiency."*

What's driving the trend to emerging markets? As biopharmaceutical companies continue to struggle with the rising cost of drug development, they are challenged to improve productivity and efficiency, streamline clinical trials, and meet more rigorous regulatory and quality assurance requirements in order to sustain profitability — in essence, to achieve far more for less cost. To that end, many are implementing strategies to boost profit margins while reducing fixed and variable costs. As part of their strategy, they are looking to emerging market CROs to help them meet these challenges.

While there are valid concerns about globalizing clinical research, emerging markets such as China, Eastern Europe, Turkey, Argentina, and Brazil play a critical role in advancing medical science. Emerging markets offer a number of attractive features, such as the potential for reduced R&D costs and development time and the availability of a large, affordable talent pool with nearly comparable technical capabilities and skills.

As the trend to globalization of clinical trials continues, sponsors and their CROs seek new solutions to lower costs and improve trial efficiency. Along with fierce competition today for clinical trial sites and an escalating number of clinical trials, they face strong competition for patients in certain therapeutic areas, increasingly complex trial protocols, and increased regulatory requirements. The cost and time to secure well-qualified sites and enroll patients have soared.

For clinical trials, emerging markets offer attractive features, with the potential for faster, less costly clinical trial enrollment and more cost-effective trial conduct. Typically, these markets also have a larger, clinically naive patient population as potential trial subjects than established markets such as the U.S. and Western Europe, and offer a means of streamlining trial costs.

For the minority of sponsors (12 percent) who have not considered outsourcing projects to emerging market CROs and/or CMOs, more than half (57 percent) are primarily concerned that the quality level is too risky, and more than one-third (36 percent) say the logistics are too complicated. Other concerns were regulatory compliance (29 percent), intellectual property (14 percent), and communications challenges (14 percent).

According to the survey, global sponsors that outsourced clinical trials to CROs conducted considerably fewer of their outsourced trials in the U.S. and Canada in 2015 (19 percent) than in 2014


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(31 percent). India and Western Europe also decreased as locations selected for clinical trial outsourcing (18 percent to 11 percent and 14 percent to 10 percent respectively). Clinical trial outsourcing continues to rise in China (15 percent in 2014 to 18 percent in 2015) and more than doubled in Argentina and Brazil (7 percent to 15 percent). Outsourcing trials also increased in Eastern Europe and Turkey (9 percent to 10 percent), the Middle East and Korea (both 2 percent to 6 percent), and Thailand and Vietnam (1 percent to 5 percent). (See figure 1.)

Countries in emerging markets are subject to the same global standards for clinical trials. Local governments have supported the trials, making efforts to improve their business environment and regulatory adherence.

COMPARING QUALITY, REGULATORY, AND AFFORDABILITY OUTSOURCING DRIVERS

The Nice Insight survey compared the performance of global CROs that have expanded clinical trials to emerging markets to see how their quality, regulatory, and affordability outsourcing drivers compared to the CRO benchmarks and how performance changed from the previous year. Looking at the 2015 clinical research benchmarks for the CROs included in the study, the guiding score for affordability was 79 percent, quality was also 79 percent, and regulatory was 84 percent. These benchmarks are higher than the 2014 levels, with regulatory increasing by 10 percent, affordability up 9 percent, and quality up 7 percent.

When comparing the scores of global CROs with these benchmarks, we found no significant differences in these outsourcing drivers. In 2015, the CRO scores were only 1 to 2 percent below the benchmarks. Looking at the changes in the average score from 2014 to 2015, the data shows a positive shift for regulatory and quality while scoring 2 percent below the 2015 benchmark and improved affordability while scoring 1 percent below the benchmark. These score analyses imply that choosing a global CRO for outsourcing clinical trials to an emerging market is a low-risk approach to addressing both cost savings and securing the targeted patient populations.

FDA regulations require that foreign clinical studies of drugs or medical devices follow good clinical practices (GCP) FDA guidelines. The FDA also requires review by an independent ethical committee (IEC), which should reduce concerns about unethical or poor quality research. In addition, major global pharma companies are increasingly looking to outsource costly pharmaceutical research and development as well as manufacturing to emerging markets, especially for small molecule drugs. Consequently, emerging countries are rapidly gaining strengths in these areas.

A 2015 report by Research and Markets forecasts that the global clinical trial service market will likely reach more than $64 billion by 2020, up from $38 billion at present, and nearly three-fourths of trials will likely be performed by CROs. While developed countries still dominate the global clinical trial market, the global clinical trial service market is split between the developed countries and emerging markets.

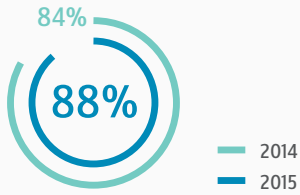
The report also forecasts that by 2020, emerging countries combined will likely account for 25.2 percent of the global clinical trial market, up from 15.7 percent at present.

More and more trials now include global trial sites, and increasingly more drug development is being outsourced to global CROs. Large global CROs that are already well established in emerging markets are well positioned for success in the increasingly competitive biopharmaceutical industry.

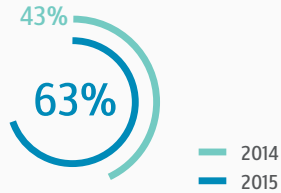
If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, at That's Nice by sending an email to nigel@thatsnice.com.

FIGURE 1 Sponsors Not The Only Party To Benefit From Clinical Trials In Emerging Markets

Respondents Considering a CRO in Emerging Markets



Respondents Already Working with CROs In Emerging Markets



Respondents Outsourcing Clinical Trials to the Following Regions (%)

	2014	2015
US & Canada	31	19
India	18	11
China	15	18
Western Europe	14	10
Eastern Europe & Turkey	9	10
Argentina & Brazil	7	15
Middle East	2	6
Korea	2	6
Thailand & Vietnam	1	5

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

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Record Funding Year Changing How Companies Access Capital

JIM PATRICK

Jim Patrick is publisher of *The Life Sciences Report*, an online investor publication that aggregates expert commentary on small- and mid-cap companies in the biotech and medical device sectors. To find out more about the 50,000 retail and institutional readers of *The Life Sciences Report*, email cbealamaro@streetwisereports.com.

I don't have to tell you that drug development is a lengthy and costly process. Recent estimates put the price tag of moving from preclinical research through human trials and the approval process at anywhere from $350 million to more than $5 billion, depending on the therapy and the scope (and whether the estimator is including in the average the costs for drugs that fail to make it through the process). Biotech stocks have been darlings of the capital markets in the last few years, and 2014 was a banner year for raising money with almost $9 billion pouring into the space. But the seemingly insatiable demand for money to develop new drugs requires a variety of funding sources with different entities serving different purposes at different points in the development process. As publisher of *The Life Sciences Report*, I get to talk to top experts in the space every day – analysts, fund managers, and company executives. I polled some veterans in the trenches and asked about the unique role each funding source plays in developing drugs today, and I found surprisingly honest answers.

VCs/ANGELS

Venture capitalists and angel investors are often the first into deals after friends and family. They often provide seed funding, advice, connections, and validation to early-stage companies. As WBB Securities Managing Partner, Steve Brozak, put it, "The goal of VCs is often to put the package together, wrap it up, and prepare it for the public markets."

Last year was a high point for both first-time and follow-on funding, according to a MoneyTree Report from PricewaterhouseCoopers and the National Venture Capital Association. First-time funding totaled $1.1 billion, a 25 percent increase from 2013. Subsequent rounds of funding brought in $7.5 billion, a 29 percent bump. That attention showed up in the IPO market. A total of 71 biotech companies launched in 2014, including the much-heralded Kite Pharma (KITE:NASDAQ), Bluebird Bio (BLUE:NASDAQ), and Juno Therapeutics (JUNO:NASDAQ) debuts.

Venture capitalist and senior managing partner of Aisling Capital, Dennis Purcell, told me that the process of going public has changed substantially over the last few years as the Jumpstart Our Business Startups (JOBS) Act made the process easier. "Companies attempting to go public were better funded because they were able to test the waters ahead of time," he said. As the sector has grown, attracting analyst coverage and telling the story to investors in a compelling way has become one of the keys to standing out in a crowded space.

BIG PHARMA

Partnering is also fueling the rise in IPOs. Brozak estimated that 10–20 percent of newly public companies have either direct or indirect support from large pharmaceutical companies. He pointed to Celgene Corp. (CELG:NASDAQ) as an innovative big company that seeded a whole bunch of companies while getting dibs on the technology if they succeed. "This is a company that understands that you get value by encouraging innovation. It doesn't have to be innovation that literally is in your parking lot. It can be innovation that you telecommute to or that you work with. The thing that the IPO market demonstrates — and demonstrates well — is that there is innovation out there. The reality is that the majority of these seeds will not succeed. But our healthcare system relies on scientific innovation. We cannot afford routine medical scientific discovery. It has to be innovative change disrupting the status quo in healthcare."

Reni Benjamin, an analyst at H.C. Wainwright & Co. and a member of the 2015 *Life Sciences Report* Small-Cap Biotech Watchlist panel, said, "The funding cycle over the last couple of years has left many small-cap companies in a

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much better financial position than they ever have been in. That's very good from a development point of view, because a lot of the small-cap companies we cover are running the right-sized trials. Small-cap biotechs are running randomized Phase 2 studies that allow us to make much more educated and confident bets on products going forward."

Not just any partner will do, however. Yale Jen, senior biotechnology analyst at Laidlaw, explained the partnering strategies for large pharma companies with thinning pipelines. "Larger drug companies nowadays are more focused and understand that synergy is important. They want to stay in the markets where they can leverage their current or expanded sales forces."

FOUNDATIONS/NONPROFIT ORGANIZATIONS

I also talked to Tracey Mumford, who works on behalf of The Michael J. Fox Foundation and sometimes with preclinical companies to promote Parkinson's disease research. Since 2000, the foundation has funded more than $450 million in research, but Mumford sees her role as more than just check-writing. Before funding a project, she often works with the company to develop a project plan that lays out milestones that should be achieved over the course of the grant and ties payments to those scientific milestones.

Brozak sees the role of foundations as significant for clinicians that need money to run very early experiments. "That is an incredibly important role," he said. "Discovery that's truly scientific is random. That's how you get the most shots on goal. Some remarkable oncology discoveries have come from research funded by foundations and not-for-profits." He does not see the money making a big impact on company development, however.

GOVERNMENT GRANTS

Government grants can be an important source of non-dilutive funding. Brozak estimated that the National Institutes of Health and the Biomedical Advanced Research and Development Authority together have fostered more scientific discoveries than any other enterprises in the history of the world. "You have to understand the system. If you think you're just going to write a grant and get cash mailed to you, you've got another thing coming. But because government grants are so specific and so demanding, they also act as a legitimizing influence, leading to more investments," he said.

GENERALIST INVESTORS

As the sector has continued to hit stock market highs, generalist investors have moved into the space, pushing up stock prices and concerns among some people that these investors are fickle and do not understand the science well enough to discern the best stocks, thereby adding to the volatility of the space. Purcell is of the mind that if companies continue to show scientific progress, generalists will remain interested in the sector, and those curves can be smoothed out. "Now that they have had such a good run with biotech over the last year or two and are seeing start-ups mature from science projects to real companies with products on the market, generalist investors don't have to understand the scientific underpinnings. They can simply look at how the drug is doing in the marketplace and what it's doing for patients," he said.

INSTITUTIONAL INVESTORS

Brozak believes there are two types of institutional investors. Sector-specific investors and crossover investors or momentum players. "You'll see them on TV, and they'll talk about healthcare in one second, and they'll have a cue card that will allow them to pronounce the name of a new drug. Then 10 seconds later, they'll be talking about movie theater revenues and the quote of a roundtrip airline flight from here to Los Angeles. What they are doing is fostering aggressive speculation and not helping anyone."

Often a stock has to reach a certain size threshold to turn the heads of large institutional investors, but they can have a big impact when they move in and when they move out of a stock.

"Many of the experts I work with see an upbeat life sciences funding market remaining in place for the foreseeable future."

TRENDING DOLLARS

Sometimes funding is subject to trends in therapy-area popularity. Brozak put chimeric antigen receptor T-cells (CAR-T) at the top of the list of research getting funded right now. "If you can spell CAR-T, you're getting funding," he said. "It is the very definition of disruptive technology." He also pointed to regenerative medicine and infectious diseases as popular areas for investing right now.

Many of the experts I work with see an upbeat life sciences funding market remaining in place for the foreseeable future due to everything from scarcity of innovation in Big Pharma to a maturing understanding of the science in areas like cell therapy and a friendlier FDA approval process. But even if the upward trend in approvals and valuations slows, good companies will continue to find ways to fund new therapies. As Brozak pointed out, bear runs — times when investors step back and stock valuations slow down or even go negative — are like safety valves. They are a reality check that ensures dollars are going to companies that can really be successful. And, they position the right companies to succeed when the bull market emerges once again.

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GUIDING BAYER'S GLOBAL INNOVATION ENGINES TO New Heights

ROB WRIGHT Chief Editor @RFWrightLSL

A little over a year ago, Kemal Malik received some really good news — he'd been promoted. The former head of global development and chief medical officer in the pharmaceuticals division at Bayer AG had been appointed to the company's five-member board of management. If you have ever received similar news, you probably recall the initial feeling of euphoria. Then as you begin to settle in to your new role, if you're not careful, this sensation can quickly be replaced by self-doubt, as you come to understand the full scope of your new responsibilities. Being a board of management member at Bayer means you are responsible for the day-to-day operations of this 118,000+ employee company. In his new role, Malik also has regional business responsibility for North and Latin America. But, during our interview he explained to me that he devotes nearly 70 percent of his time to leading the global innovation engines of the 150+ year-old company.

KEMAL MALIK
Board of Management at Bayer AG

I was curious as to what exactly that role entails. After all, innovation means something different to everyone.

What Is Innovation?

"You know, it's funny," says Malik, upon being asked to define innovation. "It's such a really hot topic in the industry. But when you ask people what innovation means to them or even just what innovation is, they get a confused look on their faces. They have a tough time explaining it." Thus, Malik says after assigning a top executive to focus on innovation, thereby endorsing its importance from the very top of a company, the next step is to define this concept.

He describes asking how innovation should be defined *by* and *for* his organization. "It's really simple," he smiles. "Innovation at Bayer is about turning a new idea into something meaningful for customers that they would appreciate." He stresses the customer piece is the fundamental component to innovation at Bayer. "Without connecting to the customer, you risk becoming too theoretical about innovation. It's not about having really smart ideas. It's about linking those ideas to insights gained from the customer."

Having a formal definition in place, Malik then considers what levels of innovation, and how much of each, would be appropriate for Bayer. He says the company categorizes innovation into three types: game-changing, sustaining, and incremental." Game-changing innovations are fundamentally new business models," he explains. "While there are fewer of these types of innovations, they are important because they may be truly transformational to your business.

Sustaining innovation refers to new products and services and is critical to the continuity of any company. The third category is incremental innovation. "This involves process improvements, product life cycle management, and enhancing the features of our existing products," he states.

Malik says Bayer spends about 70 percent of its R&D efforts and resources on the sustaining innovation category, with the remaining 30 percent of innovation resources fairly equally distributed between game-changing and incremental efforts. "Too much game-changing innovation is too risky and may challenge your sustainability," Malik reminds. "Conversely, it can't just all be incremental, because you may miss some huge move that can destroy your business."

Malik's Non-Negotiables For Reviewing A Game-Changing Innovation Proposal

As Bayer is a $47 billion+ company that annually invests around $4 billion in R&D, innovation leader Kemal Malik admits that not every innovation proposal comes across his desk, and those that do, are usually of the game-changing, high-risk variety. "It's difficult always to find these potentially game-changing, high-risk things fitting into the normal structure processes and funding mechanisms one uses for sustaining and incrementally improving innovation," he says. "A board needs to be open to hearing about these kinds of game-changing innovations, even though probably 90 percent of them may not transpire." To determine if your "game changer" needs board-level review, first determine the elements of risk associated with the investment required. "If it has high risk but requires very little money, they probably won't bring it to my attention," he says. "Conversely, if it's very low risk but requires a lot of money, it may well come across my desk. However, low risk signifies it is most likely not a game-changing innovation, so make sure you are classifying your innovation appropriately. "Game-changing innovations typically involve a lot of risk and require a significant investment [e.g., $10 million to $100 million]," he says.

So what "non-negotiables" does Malik look for when reviewing game-changing proposals? "First, what's the value for the customer?" he asks. "I always insist the teams go through the discipline of explaining this. It sounds easy, but sometimes people get too caught up in the excitement of the science, process, or technology as being so cool and cutting-edge that they lose sight of how this change will be valued by the customer." According to Malik, if the customer doesn't value it, then it isn't actually true innovation by Bayer's definition. "That's non-negotiable for me. It's not about the cost, resources, or the time frame, but have you really thought through what this means for the customer, and can you explain that to me in a few sentences?" For example, Malik recalls the company coming up with what it thought was a cool technology system to improve oral contraceptive compliance for women. "We really didn't spend enough time talking to ladies about how this would fit into their handbags, their lifestyles, because we got so excited about the compliance benefit," he admits. Although Bayer did some customer testing, Malik believes it was probably not enough, because customer acceptance wasn't as high as they thought it would be when the product came out.

On the other end of the spectrum, Bayer developed a new blood thinning drug, Xarelto, which has become one of the company's most successful compounds. "We knew we were entering a very competitive space," Malik states. "We spent a lot of time talking to doctors asking what they would look for in an ideal blood thinner." He says what doctors were clearly looking for was a requisite degree of efficacy and safety in the prime indication where the drug would be used (i.e., prevention of strokes in patients with atrial fibrillation). They also said these patients are typically older, and a once-daily formulation would be great. "Oh, and another thing, we want to get used to using one drug in all the indications where we want to use blood thinners and anti-coagulants," he continues. "If you developed this for a patient undergoing orthopedic procedures to prevent a blood clot, in a patient who's got an existing blood clot, and in stroke prevention in atrial fibrillation, we would have a wide range of indications where the drug can be prescribed at the time of launch, which would be very meaningful." Given the drug's success thus far, Xarelto serves as a great example of the value of not only speaking to your customers but also of being prepared to figure out ways to do what it is they are asking for.

Guiding Innovation From The C-Suite

When it comes to guiding Bayer's innovation engines, Malik approaches it via (1) leadership and strategy, (2) structure and processes, and (3) people, values, and culture. Leadership is responsible for demonstrating from the very top why innovation

is important, ensuring the appropriate funding and metrics are in place, and making sure that people understand the innovation portfolio (i.e., game-changing, sustaining, and incremental). "Only then can you drive the specific initiatives," Malik states. The second means to driving the innovation engine is to have the appropriate structure and processes (which we will get into a little bit later). But Malik cautions that too much process can be a bad thing. "You need process, because otherwise we have anarchy," he attests. "But if you have too much process, people are spending all their time managing the process rather than coming up with good ideas." The third piece is people, values, and culture, and for Malik, this is the most important. "It's often said that culture eats strategy for breakfast," he recalls. To create a culture in which people feel innovation deeply, Malik says you have to engender a culture where people want to try new things. "There needs to be a tolerance for failure and a willingness to experiment so people aren't afraid to take a few risks." Malik views innovation and failure as strange bedfellows. "If you never have any failure, you're probably not innovating enough," he affirms. "However, you should know how to learn from failure." To learn from failure requires two things —conducting a lessons-learned exercise and using restraint on punishment. "If a team has failed on a project, punishing the people who worked on that project is a surefire way of stopping them from ever trying anything new again," he says.

In 2013 (before Malik was appointed to his current role), Bayer began working with innovation thought leaders at London and Harvard business schools. The result of these discussions was a series of two-day workshops on the topic of innovation that were mandatory for about 400 of the most senior people at Bayer. The program included employees from various divisions/departments (e.g., manufacturing, finance, legal, R&D). "We wanted to send a message from the boardroom that no matter where you work, no matter how busy you are, as the most senior leaders in our organization, you need to attend these workshops. This is how important *everyone* is in driving innovation at Bayer," says Malik.

Beyond sending a message, Bayer came away with a number of tangible outcomes from these workshops. "We developed something called the systematic innovation toolkit, which we utilize across the organization," he shares. For people who have spent the majority of their careers in R&D, a toolkit on how to encourage innovation probably seems silly. But what Bayer and Malik learned from the workshop was that in different parts of the organization outside of R&D, when people wanted to try new and innovative things, they often struggled with how to get started. The innovation toolkit provides the structure necessary to allow the unsaid to be said. "The worst thing for driving innovation is a person who says, 'You know what? I've been here 20 years. We tried

that in 1996. It didn't work. Forget that, and move on,'" Malik attests. The toolkit provides the structure on how to manage these types of idea killers as well as ways to start the innovation process.

In addition to the toolkit, the company also developed an internal platform called "We Solve" that allows Bayer employees to post a challenge, perhaps something they are struggling with in their jobs. Some examples include questions such as, "How do you take ideas generated, move them forward, and then convert them into action in order to maximize their value?" "What decision-making do you need day to day? How are you going to fund it? How can you ensure that you get the most out of that idea?" Bayer employees worldwide can help to come up with solutions to these kinds of questions.

Another outcome from the innovation workshops was the development of the Bayer Open Innovation Center in Japan (ICJ). Launched on June 1, 2014, the ICJ is focused on identifying potential collaborative research projects in Japan (e.g., the two-year collaboration agreement between Bayer and Kyoto University's Office of Society-Academia Collaboration for Innovation [KU-SACI]).

Bayer's Innovation Structures

At Bayer, there exists a number of structures to facilitate innovation, such as communities and committees. Malik describes innovation communities as being less formalized, providing the opportunity for people who work in broadly different Bayer businesses but with functionally similar responsibilities to network and share best business practices. "Different parts of our businesses inevitably have different levels of maturity, sometimes different degrees of customer intimacy, for example," he explains. "Our consumer care OTC business has been dealing directly with the end purchaser of our products for a long time. As patients are becoming increasingly important in driving decisions in pharma, our pharma people have been spending a lot of time with our consumer people." This innovation community is helping to facilitate the knowledge transfer of how the consumer business captures insights from the end user, so the pharma business can incorporate into how it engages with patients and thus, improve Bayer's R&D activities. While these innovation communities conduct a lot of activities virtually, Malik says they do usually meet in person at least twice a year.

Innovation committees at Bayer are more formalized and bring a slightly different group of people together. Consisting of about eight people, these groups meet once a quarter for an entire day to discuss common issues they face. One of the groups is an innovation research committee with senior people from pharma, crop science, and material science research. "These are not the heads of research but people a level below," Malik explains. The committee has a rotating chair facilitating the meetings. Ideas gathered from these get-togethers are passed on to Malik through an innovation strategy group which reports to him directly and for which he serves as chair. One of the best practices resulting from the innovation research committee involves the use of interdisciplinary project teams. "One of the fundamentals of how we run R&D activities in our pharmaceutical business was the interdisciplinary project team, which typically consisted of someone from all the various disciplines — research, development, clinical, medical, toxicology," Malik explains. He says since learning of this approach from this committee, crop sciences has begun integrating interdisciplinary project teams into its R&D programs. "We're finding that one part of our organization has a lot of specialized experience which can help other parts of our organization do things differently," Malik affirms. "We're making better decisions because various people from different disciplines are discussing the same issue."

Malik subscribes to the notion that great ideas can come from anywhere. "Innovation isn't the domain of internal R&D," he says. "Our obligation to our company, to our shareholders, to society, is to get those ideas into our company and then see if we can convert them into something meaningful for our customers. That's what I really want to push in our organization when it comes to innovation." L

When Leading Innovation, Actions Speak Louder Than Words

Being responsible for global innovation at Bayer, Kemal Malik realizes the importance of consistently communicating the value of innovation, not just with words, but actions. For example, in early February, Bayer conducts Innovation Day. The board of management goes offsite and is joined by the heads of the various Bayer businesses (e.g., healthcare, crop science, etc.). "We spend a day just talking about innovation," Malik shares. "While this informs the board of current innovation-related activities, it also reinforces the message of how important our leaders' actions are in relation to furthering our focus on innovation." He says many leaders underestimate the power of their behavior to send signals throughout the organization. "The way you do things, the way you act, the things you say as a senior leader, influence the organization," he affirms.

As an example — and also as a warning regarding the importance of managing your time appropriately when it comes to innovation and leadership — Malik shared that Bayer has created an area where start-up companies can come in and use Bayer facilities free of charge. When he visited the area recently, he was intent on being there for only an hour, but he ended up staying for more than three hours. "Smart kids in their jeans and long hair who have these start-ups for digital and healthcare apps — they were just so fun to talk to about their ideas and what they wanted to do," he confides. "Yes, as a leader you have to manage your time effectively, but you've also got to allow yourself the time to do these sorts of things." His rationale as to why is twofold. First, it invigorates you personally about your own job. Second, and to his earlier point, don't underestimate the power of your behavior to signal and influence people throughout your organization.

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HARMONIZED POST-APPROVAL CHANGES:

A Vaccine For Global Drug Shortages

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"It's true," confirms Anders Vinther, chief quality officer at Sanofi Pasteur and a long-time chairman at Parenteral Drug Association (PDA), "global regulatory agencies have only now started to address the subject of harmonizing global post-approval change applications for drugs."

These post-approval change (PAC) applications are required for the introduction of process or analytical modifications or new manufacturing facilities and advanced technologies to improve and more reliably produce drugs already on the market. It's hard not to be a little disappointed upon learning that not much progress has been made regarding global harmonizing — or standardizing — of the different PAC requirements for individual countries or regions. It feels like an example of myopic regulatory drug agencies being unable to see the forest through the trees. Vinther, though, is an optimist who views this start as a welcome opportunity. "We are at a tipping point, and we need to work together," he says. "Our industry has done well not to shoot at global health authorities along the way, because you get nothing out of that." He adds, "There could be arrows on both sides."

Drug Shortages: A Tipping Point And Quivered Arrows

The main driver of the tipping point for harmonizing global PAC applications is drug shortages, which have increased in number, severity, and the fear surrounding them. At this point, reproach slung from either side would make drug regulators and biopharma manufacturers combatants instead of companions. Vinther, in his role at PDA, has been a champion of collaboration. He says both camps now realize drug shortages and PAC regulations go hand-in-hand.

For their part, global drug regulators have raised expectations that manufacturers do more to proactively predict and prevent issues that lead to drug shortages. These agencies are also starting to move toward more structured national or regional requirements for notification of changes in facilities and equipment and other supply chain events. On the other side, biopharma has become more direct in explaining to regulators that drug shortages can be caused, in part, by policies set by the regulators themselves. The most egregious of which remains this lack of harmonization of the PAC application processes.

"That's where we stand right now," says Vinther. "We agree biopharma manufacturers need to be better at anticipating the risk of a drug shortage from a company perspective. We also need health authorities to find ways to expedite and harmonize the process for introducing changes that improve process variability and the quality of products, in particular when this can enhance drug supply."

The current situation is indeed an opportunity for both sides to share responsibility and implement measures to improve drug supplies for patients. PDA is one group at the forefront, providing a forum to spur some of these activities. It has 10,000 individuals from all segments of healthcare, including many drug regulators, according to Vinther. PDA recently released a technical report for the biopharma industry that is a "how to" on avoiding drug shortages. A second initiative underway at PDA and led by Vinther, who has passed on the active chairmanship role and now serves as an Immediate Past Chairman, is called the "Global Change Protocols for Comparability Studies." This is aimed directly at drug regulators to assist in harmonizing PAC applications.

"The technical report first says, 'Okay, let's address what we can in our own house,'" explains Vinther. "The Global Change Protocols will then suggest a positive way for biopharma and regulators to work together to define and harmonize PAC requirements. Both documents are based fully on science, not politics."

The report is officially titled, "Technical Report No. TR 68: Risk-Based Approach for Prevention and Management of Drug Shortages." Vinther describes it as a fully developed, structured document and practical technical outline for biopharma to go through product portfolios to identify and mitigate the potential for drug shortages.

The upcoming protocols document is a hands-on attempt to jump-start the process of harmonization. "Everybody around the table now says the current situation is not sustainable," says Vinther. "Shortages are now a global patient-critical issue."

Vinther says the initial technical report has been well appreciated by both the industry and regulators, who have posted it on their websites to demonstrate their encouragement for biopharma adoption. The European Medicines Agency (EMA) may go further. "They may introduce it as a part of their regulations," says Vinther. "The dialogue is better now. They see we are answering their call to address concerns."

Let's look, then, at what a company like Sanofi Pasteur faces in the current regulatory environment and what global PAC harmonization would actually mean in practice.

Vaccines Made More Difficult

Creating vaccines is akin to trying to hit a moving target; the product has to change as the target does. Sanofi Pasteur, the vaccines division of parent Sanofi, is today the largest company devoted entirely to human vaccines. It produces a range of vaccines, including those for 20 bacterial and viral diseases, and it distributes more than 1 billion doses each year, making it possible to vaccinate more than 500 million people around the world.

But vaccines have become a low- or no-margin business, and perhaps the best example of how biopharma is hurt financially by the checkerboard of regulations spread across the globe. Just this January, while attending a Gavi Global Vaccine

Anders Vinther, despite the long hours and travel dedicated to his work at PDA, and of course his position at Sanofi Pasteur, does have a pastime, one he's equally passionate about and one not out of character: He's owner of Flying Suitcase Wines, a vineyard in San Carlos, California. Vinther is Danish by birth, received his Ph.D. in chemical engineering at Danmarks Tekniske Universitet, and started his career at Novo Nordisk. He currently lives in California near his vineyard. There's certainly an art and science to bottling high quality wines. For one thing, we can be assured he has less paperwork and fewer regulatory bodies to deal with in producing fine reds and whites. And if there ever were shortages, they'd be mostly caused by acts of Mother Nature. In contrast, and in all seriousness, the potential vaccine and other drug shortages facing patients around the world today appear to be mainly man-made and solvable in great measure by industry and regulators harmonizing post-approval change (PAC) applications around the globe. Let's hope the challenges hampering the efforts of Vinther and so many others are eradicated like some of the diseases they vaccinate us against.

Alliance meeting in Berlin, philanthropist Bill Gates dismissed criticism by health campaigners of the perceived high prices of some vaccines, according to *The Guardian*. Gates warned it only serves to deter pharmaceutical companies from working on life-saving products for poor countries. (For a look at more factors that have led to this point of increasing risk of drug shortages, please see the inset article.)

In fact, Sanofi Pasteur and other vaccine manufacturers increasingly find themselves the only, or one of few, who produce a certain vaccine for global markets. Others have been driven out of the business by intense price competition and price pressures from healthcare organizations and the complexity of making and getting vaccines approved. For example, each time even a minor change is made to how a vaccine is produced, the company must submit hundreds of PAC applications, all with different requirements, to each country where that product is available. Because of this and other factors, in the worst cases, global supply of some vaccines is down to one or two manufacturing facilities.

Vinther offers the example of a conventional manufacturing — or filling — line currently in a classified cleanroom but with some open operations. Moving from conventional filling to the use of isolators would reduce any risk of contamination and other sterility assurance issues. "This, of course, is a great change," says Vinther. "However, each country has its own procedure for approval. You can imagine a company operating in a hundred countries and dealing with a hundred applications for the health authorities to look at things differently. While the requirements for each country may make sense, collectively for the company, this complexity of filings can stifle innovation and the introduction of new technologies."

The unrealistic expectation of this current process is the production of the same product in a variety of different ways. "Companies get bombarded," says Vinther. "Country A has approved, so now we must manufacture the new way, but Country B has not approved, so we need to continue using the old technology. As a company, you just want to continue to improve. The objectives are the same for patients, health authorities, and companies: safe, high-quality products, everywhere. Right now we have a logistics nightmare."

Consider the simple example of the common but complicated vaccine DTaP (diphtheria, tetanus, and whooping cough [pertussis]) booster immunization shot. It consists of a variety of strains that have to be kept current, from both a strain and manufacturing point of view. According to Vinther, a DTaP booster might require 15 different manufacturing processes. A change of any kind requires an application to each of the hundreds of health authorities.

For a separate vaccine, Vinther said a company once counted it needed 55 different variations to produce just under

HOW DID WE GET HERE?
Four Errant Steps To Drug Shortages

Anders Vinther, chief quality officer at Sanofi Pasteur, and long-time (immediate-past) chairman at Parenteral Drug Association (PDA), points to four factors leading the world down the path to drug shortages.

In some ways, the first is the most difficult to understand. Free markets and competition are the very stuff of capitalism and should lead to innovation, more supply, and yes, lower prices. But hyper-price competition has now even reached generic/biosimilar players, who are partly based on win-on-price business models. "Go to your local pharmacy," suggests Vinther. "Over-the-counter drugs are sometimes cheaper than a 6-pack of bottled water." He says for drug manufacturers today, selling into healthcare organizations can leave little – or no – profit. This drives companies out of the market and leaves patients with one or two manufacturers, and at times one facility, manufacturing drugs they need.

"The industry has changed," says Vinther. Pharma finds itself manufacturing many drugs with little or no margins and no supply elasticity. What else has changed has to do with our initial premise of free markets. With increasingly socialized healthcare systems, powerful intermediaries, and government intervention that brings with it concern for political outcomes, the healthcare industry is far from any status of free-market principles.

Another reason for drug shortages is that while both demand and requirements for production are increasing globally, funds for investing in infrastructure at manufacturers is decreasing (see directly above). Drug manufacturers can fall behind in meeting requirements, and making the upgrades that in turn lessen supply pressures. "Equipment gets outdated, new facilities are needed, and you might see skilled-employee turnover in a certain area; many reasons directly related to manufacturing quality lead to drug shortages," says Vinther.

This prompts authorities – already scrutinizing manufacturers – to place even more attention here. "Government regulators say to manufacturers, 'You need to do everything you can to predict supply issues,'" says Vinther. As we documented in our main article, the industry is serious about the need for a greater level of risk management to avoid drug shortages. Manufacturers, though, know fewer problems would occur if there were an understanding of the impact of the constraints they are put under in the first place, both requirement- and market-wise.

A third cause, of what can be identified as "isolated" shortages, and perhaps the least known or understood, is "parallel trading."

The World Health Organization (WHO) describes the phenomenon of parallel importing this way:

> *Parallel imports are imports of a patented or trademarked product from a country where it is already marketed. For example, in Mozambique 100 units of Bayer's ciprofloxacin (500mg) costs US$740, but in India Bayer sells the same drug for US$15 (owing to local generic competition). Mozambique can import the product from India without Bayer's consent.*
>
> *According to the theory of exhaustion of intellectual property rights, the exclusive right of the patent holder to import the protected product is exhausted and thus ends when the product is first launched on the market. When a state or group of states applies this principle of exhaustion of intellectual property rights in a given territory, parallel importation is authorized to all residents of the state in question. In a state that does not recognize this principle, however, only the patent holder who has been registered has the right to import the protected product.*

"I've experienced this with my work in the European Union," explains Vinther. "One country has plenty of supply for pharmacists for a certain drug. But a second country in Europe starts buying up the supply because it can actually purchase it cheaper by a parallel import. Suddenly the first country, which had all the drugs it needed, doesn't anymore."

Parallel imports are also referred to as the "grey market." Remarkably, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement specifies this practice cannot be challenged under the World Trade Organization (WTO) dispute settlement system. This allows the practice to continue, and according to Vinther, adds to unnecessary drug shortages.

Our fourth reason for drug shortages is the topic of our feature article, the inadequate harmonization for post-approval changes. These are not the only four. However, the common thread of these we've outlined is pricing pressures on BioPharma to discover, develop, manufacture and distribute more drugs anywhere in the world ever more cheaply. This seemingly incessant demand for lower prices comes from legitimate market forces – although normal supply-and-demand mechanics seem no longer to operate in healthcare – and less legitimate non-market, outside forces and manipulation.

Perhaps here's the bottom line: There is no free ride to improved healthcare and medicines. No industry — providers of home-heating oil, assisted-living facilities, transportation companies — can operate at no profit and continue to provide products and services.

Time will tell if we are demanding that some drugs cost so little we'll end up paying a much dearer price later. Drug shortages are a first and troubling sign we are getting there already.

90 batches of product. "Intellectually, let's all think about it," he suggests. "If 59 countries have approved a vaccine-manufacturing change, what would country number 60, 61, or 62 add that the others didn't?"

Finally, we should note that in Europe, for example, it is a legal requirement that manufacturers consider new technologies, like the isolator we mentioned above. On the surface, this sounds like a reasonable and forward-looking policy. And it is, in isolation (forgive the pun). But, if an advancement is made for Europe, this necessitates that PAC applications be submitted around the world to raise all standards. Is this protecting or harming healthcare systems and patients?

Patients Should Know

The magnitude of this challenge with PAC processes is only partially known to patients around the world. The question is how to inform them and bring them into the discussion.

"Every decision I make, I make thinking of what is best for the patients," says Vinther. "It used to be straightforward for a quality professional to reject a batch, even for a minor violation of procedure that was shown not to affect quality. It's not good financially, but it's an easy decision to make. The hard part right now is that if I reject that batch — perhaps an environmental monitoring sample was not properly taken — I know there are patients who will not get their drugs. That is a difficult dilemma to be in today."

Vinther continues: "Patients don't necessarily appreciate the full complexity of manufacturing; their concern is their health, and rightly so. But the dialog among regulators, the industry, and patients is important because we really need to understand we all have one common objective — the availability of medicines to all in need."

However, approaching patients and patient advocacy groups regarding regulatory and manufacturing issues — even related to drug shortages — can be difficult for biopharma. There is the risk of being accused of "politicizing" issues. Patient organizations inherently have a focused agenda. "This is the closest you can get to people not continuing the life that they have because they need medications," says Vinther. In an era of 24/7 social and traditional media, no organization wants to be seen as trying to manipulate patient opinion.

This is where Vinther sees the PDA as playing a vital role in bringing all sides together to harmonize PAC requirements and lessen drug shortages. He says that to the extent possible, PDA members check their business or organization affiliations at the door and focus on science and nonpolitical solutions. "We are made up of individuals; we also just happen to be the best experts in the world in a variety of areas in the pharma industry. This is a venue for all people to gain perspective and forge solutions based on rock-solid science." L

THE ENTERPRISERS

Agile Therapeutics: Reengineering Innovation

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

PUBLIC COMPANY: NASDAQ Global Market Ticker Symbol: AGRX

MARKET CAP: About $158 million

CASH: $45.7 million at Sept. 30, 2014

START-UP DATE: 1997

NUMBER OF EMPLOYEES: 12

FOCUS: Women's health specialty pharmaceuticals; weekly, hi-tech contraceptive designed to overcome previous barriers to use of patches

The top management team at Agile Therapeutics reflects an atypical bounty of experience and expertise for a small life sciences company. That was no accident, though it came of necessity following a near calamity. The attributes of the relatively new team proved essential in helping the company survive a key clinical trial setback that might have otherwise derailed it.

Agile's initial NDA (new drug application) for its lead product caused the FDA to issue a complete response letter that sent the company back to the drawing board in late-stage development. Then-chairman Al Altomari took over the CEO role and assembled new management, which organized a confirmatory trial of the company's new contraceptive patch, Twirla (ethinyl estradiol/levonorgestrel), now entering a confirmatory Phase 3 trial.

Sometimes, rather than creating entirely new entities, entrepreneurial enterprises innovate by leapfrogging old technology — and sometimes, by leaping ahead of their past mistakes. Agile has rallied all of its capital and resources around developing products in the almost-abandoned field of women's health related to contraception, starting with a lower-dose, more-convenient alternative to the only existing birth control patch on the market.

Altomari headed the division that brought to market the sole patch now available, Ortho EVRA (ethinyl estradiol/norelgestromin), in his former job at Johnson & Johnson, but he turned to the small-company world to push for a new once-weekly patch with a safer dose and engineered for comfort. Twirla would be the only low-dose transdermal contraceptive on the market if approved and the only one containing levonorgestrel, a more tolerable form of progestin. (See "A New Patch — Agile Upgrades Contraception" on page 38.) Agile also has additional transdermal products in development that, it says, "could offer a shortened hormone-free interval and an extended-cycle regimen of consecutive use, aiming for shorter, lighter periods and/or fewer periods."

Small companies developing new, entirely novel products all too often lose their way by focusing inwardly, without a clear plan for the long term. But almost by definition, companies like Agile, those taking an old idea and making it new, must deal early with scale-up, clinical trials design, and overall growth strategy. And their planning must include a look at external factors such as medical practice needs, reimbursement, and patient adherence. All small life sciences companies, of all types, can draw useful lessons and learn best practices from the "reengineering" enterprises.

But the ideal scenario just described does not exactly match Agile's actual history. During the years 2010 and 2011, under previous management, the company conducted its Phase 3 trials for Twirla, but the FDA sent a complete response letter saying the NDA was insufficient for approval as originally submitted. The agency recommended an additional Phase 3 trial be conducted with a simplified clinical trial design and improved study conduct. Altomari's new executive team had to figure out how to answer the agency's concerns.

"We recruited this team to move Twirla across the goal line," says Altomari. "To be candid, we could have done some things better in our previous trial, and we believe we can get this one right. We are going ahead with a blend of humility and confidence."

TRIAL BY CONFIRMATION

In some ways, the company had tried too hard to simulate real-world conditions in its first Phase 3 trial — incorporating a wide diversity of patients including a high proportion unfamiliar with any form of birth control. The FDA found the Phase 3 data too complicated by factors extraneous to the product itself. With the new confirmatory trial, SECURE, Agile aims to minimize such elements by enrolling subjects at sites that have experience in conducting contraceptive studies and by using a more experienced CRO, thereby achieving higher compliance with the protocol.

Chief Medical Officer Elizabeth Garner, M.D., explains. "Most of the issues the FDA raised in its complete response letter had to do with how the studies were conducted at the sites — too-rapid enrollment, high discontinuation rates, loss-to-follow-up rates, and other issues affecting general compliance with the drug. Our study population largely consisted of individuals who were new to hormonal contraception, people who face a learning curve and generally will not do as well as experienced patients. The agency had a tough time interpreting our data given the number of patients we had lost from the studies."

Some good news came out of the first Phase 3 trial, Garner says: "We believe the agency seemed sufficiently comfortable with Twirla's dosing and its safety profile. That's huge for us, especially with EVRA in the background. So they asked us to do another trial and focus heavily on the study conduct."

Thus, says Garner, the company has several reasons to think the new trial will be successful. First, its new CRO, Parexel, has sufficient "bandwidth" to handle the trial — a possible problem in the first one. Second, the few clinical sites that showed the worst compliance, dropouts, and pregnancy rates in the first trial are not participating in the second one. Third, the company has worked with Parexel to identify additional qualified investigators who can help select the patient population for the new trial. All of the measures should ensure much better compliance to give the product the best possible test of safety and efficacy as a basis for FDA review.

The centerpiece of the SECURE trial, according to Garner, is the use of new technology to gather and manage the data. For example, the trial will employ eDiaries, known to do a much better job of capturing patient responses than the old paper-based systems. (See "Direct To Data — An Electronic Solution To Patient Diaries," August 2012.) SECURE also provides trial subjects with a host of educational materials and other compliance aids.

PERSONNEL LEVERAGE

As with the eDiaries, supplied by PHT, almost all of Agile's operations are virtual. In scaling up to produce the new patch for clinical trials, the company also relied on its manufacturer, Corium, for process development and production. "We are very comfortable with outsourcing," says Altomari. "We are in a new age of virtual companies, but most of us come from Big Pharma, and we are experienced. We aim to select the best suppliers in class, with the best consultants in class, to supplement ourselves. We promise investors we will stay administratively lean. We have greatly skilled executives, but a small staff, relatively, even for a small-size company, and we like it that way."

Altomari came to Agile from Barrier

A NEW PATCH – AGILE UPGRADES CONTRACEPTION

Elizabeth Garner, M.D., chief medical officer at Agile Therapeutics, describes how the company's Twirla (ethinyl estradiol/levonorgestrel), now in a confirmatory Phase 3 trial, differs from the only current transdermal contraceptive on the market, J&J's EVRA (ethinyl estradiol/norelgestromin).

"Twirla contains two very well-known hormones, very commonly used in contraception: levonorgestrel, a progestin, and ethinyl estradiol, a synthetic estrogen, in combination. EVRA contains the same estrogen, but a different progestin, and it delivers substantially more of the estrogen on a daily basis. That is one of the major differences between our patch and the EVRA patch. EVRA has had notable problems with blood-clot risk, so we believe our patch may address that problem with its lower estrogen dose. Ultimately, we believe our patch will be shown to be safer than the EVRA patch in the risk of clotting.

"The Twirla patch is what we call a matrix patch, in that the hormones are interwoven with a number of enhancers that help the hormones to get through the skin. That is one of the interesting features about the patch that leads to a more consistent delivery of hormone through the skin, as opposed to older patch designs. There are six layers to the patch, including a peripheral backing. The material has a light, clothlike feel very different from the EVRA patch; it is very flexible, moving along with your activities. But the most unique aspect of this patch is this – hold it up to the light and you can see an inner ring, inside concentric circles, where the actual hormone is. You can barely feel it, too. What that means is the drug is contained in the middle of the patch with the adhesive surrounding it. That is very different from the EVRA patch, where there is drug all the way to the edges of the patch that can seep out when the patch is worn, getting on clothes and so on.

"This is also the first known patch to deliver the levonorgestrel hormone, a progestin responsible for contraceptive efficacy, at sufficient rates to reach contraceptive levels. The estrogen mainly controls bleeding. Levonorgestrel alone, like any progestin, can cause some irregular bleeding."

CEO Al Altomari adds a comment about the innovation required in creating the new contraceptive patch:

"The engineering of this patch is as complicated as the biology and the chemistry of hormonal contraception. Imagine a piece of cloth that's pulling and getting into folds and creases rather than settling into a nice little round circle and consistently delivering a drug. Not many companies can make patches, so there are not many drugs delivered by a patch. Our technical challenge was not to deliver estrogen, which can transport pretty easily across the skin. It is the progestin that is hard to transport. We are quite proud of this technology. We own all of the patents, so this is our product. We don't owe any royalties; this is in-house technology."

Therapeutics, where he steered the company to the point of acquisition by Stiefel Labs (later acquired by GSK). He held a variety of leadership positions at J&J from 1982 to 2003, heading the Ortho-McNeil Women's Health Care division during the commercial planning for EVRA.

He has avoided creating multiple layers of management and only added new functions as they were needed. Chief Commercial Officer Katie MacFarlane, Pharm.D., an advisor since 2009, came on board full time in 2014, in anticipation of a Twirla launch. Her role also heralds the company's strategy of full integration, as opposed to acquisition or licensing out.

"I come to work planning that we're going to launch this product," says MacFarlane. "We are doing all of the commercial prep work that needs to be done. Agile has produced more than 25 publications in the literature on this patch. We have worked with a great group of key opinion and thought leaders. We've done a lot of market research to identify the right messages in selling. We've even done a trademark. We believe we have everything we need ready to go, so that if we are granted an approval, we will be in a good position to get out into the marketplace."

The company has even planned for the sales force, as MacFarlane explains. "The great thing about the contraceptive market is it is a true specialty market. The OB/GYNs drive an enormous percentage of the prescriptions, so you can efficiently market a contraceptive with about 70 to 100 reps, and that's the model we're working under right now."

Agile is also counting on continued support from patient groups and contraception advocates. It has long-established relationships with all main women's health advocacy groups, including Planned Parenthood, NOW, The Campaign to Prevent Teen and Unplanned Pregnancy, The Black Women's Health Imperative, and the Latina Institute. MacFarlane mentions Bedsider, a popular website that presents a wide variety of birth control methods.

"These are true advocacy groups," she says. "They are great about keeping informed about policy issues, such as

insurance coverage, the Affordable Care Act, and many others that affect contraception, which enables us to stay on the cutting edge. They want women to have access to all the contraceptive options, and because the current contraceptive patch on the market is thought to be not the safest product with its high dose of estrogen, I believe they would like see an alternative contraception patch option."

"If I were at J&J, Merck, or any of the big companies, and I said to our bosses, 'Hey, we're going to go down to D.C. and hang out with a bunch of lobbyists,' I would be flung out of my job," comments Altomari. "But as a young company, we say, why can't we go down and talk to them? Why not? We are all on the edge of these very controversial issues because we believe we're developing a good product, we are advocates for women, and we're advocates for choice in contraception."

Is the precommercial stage too early to think about marketing? Altomari believes small companies typically wait much too late to do so. "We don't overspend on commercial planning before approval; everything is timed appropriately, but we come out of Big Pharma, and I would say our business plan is as good — maybe better, because we have had more time to work on it."

Altomari credits the company's survival and "second chance" at success with the SECURE trial to good cash management. "We have been very responsible," he says. "We wanted to be ready to weather the financial storms if we needed to and get through some tough times. We have been able to do that."

Resources flow to where they are needed most — clinical development. Manufacturing and commercialization, though also essential, come second. "In my mind, every dollar we would spend in overhead could be better spent in the clinic," says Altomari. "We believe our lean operations are one reason the people who invested in this company privately also invested in the company publically. Even in our IPO, private investors came forward and supported us."

> "In my mind, every dollar we would spend in overhead could be better spent in the clinic."
>
> **AL ALTOMARI**

Altomari says he is grateful the company got its second chance in life, a rare and valuable exception to the rule. At Agile, he and his team seem to have found an exhilarating balance of Big Pharma experience and small life sciences company gusto — innovating by turning the old into the new. L

More Drugmakers Dip Into Social Media To Find And Engage Patients

NEAL LEARNER Contributing Writer

Freewheeling engagement with the public is not the first thing that comes to mind when considering the pharmaceutical industry. But that's what is happening more and more as drugmakers set up social media sites that allow patients to interact with company experts and the broader community about health problems and potential solutions.

Social media has become the place to go for patients to find information and share views with others, says Murray Aitken, executive director of the IMS Institute for Health Informatics. "Pharma companies who are 'patient-centric' recognize the critical role that social media plays in healthcare and the importance of engaging with patients through those media outlets," he adds.

Taking the social media plunge, however, hasn't come quickly for an industry in which one wrong statement or omitted fact can draw the FDA's ire. At the end of 2013, just half of the 50 largest drugmakers were using social media to communicate with patients and consumers about health issues, according to a January 2014 study from IMS Institute for Health Informatics. Today usage continues to increase as companies become more comfortable with the regulatory framework for online activities and recognize the growing role that patients play in their own healthcare, especially as high-deductible plans bring more visibility to the cost of care.

DRUGMAKERS ESTABLISH RULES TO AVOID MARKETING VIOLATIONS

Some companies have jumped in with gusto. Take drug giant Pfizer, which has a strong presence on the major channels of Facebook, Twitter, and YouTube, as well as others. One of Pfizer's Facebook pages is called "Meet Meningitis," which describes itself as "your source for information about meningococcal disease." The page, which launched in November 2014, has nearly 8,000 likes and includes a wide variety of posts, videos, information, advice, and personal stories of survivors. A December 2014 post detailing statistics of meningococcal disease had been shared more than 2,810 times as of early February and generated nearly 500 comments, many telling harrowing tales of their own experiences with the disease.

But the discussion, as robust as it is, is not without parameters.

Pfizer includes a prominent section on the site that explains why the company sometimes has to pull comments from the wall. The top reason is a comment referencing a product, either Pfizer's or someone else's. "While we do not endorse any users' comments, we still have to be mindful of the important regulations that govern our industry," Pfizer says. "If your post references a pharmaceutical brand from any company — positive or negative — we will need to remove it because, among other reasons, we can't guarantee that it will represent Fair Balance." Other posts that get the chop include those that reference a side effect of a drug, offer medical advice, are off topic, or are simply vulgar.

HANDLING NEGATIVE COMMENTS

Indeed, it is not uncommon for consumer engagement to appear out-of-bounds on social media. A recent consumer posting on Pfizer's Twitter feed, for example, claimed that one of the company's drugs had turned him into a rapist. Pfizer's prompt response was to direct the consumer to the company's adverse-events reporting site. Such an exchange underscores a significant pitfall of the medium. "You can't control the user-generated content," says Jeffrey Wasserstein, a director at law firm Hyman, Phelps & McNamara, and an expert in pharma-

> *"You have to be careful because your messaging is being put out there to a much broader audience than you typically see for a promotional piece."*
>
> **JEFFREY WASSERSTEIN**
> A director at law firm
> Hyman, Phelps & McNamara

ceutical promotions. The FDA has issued guidance that basically says a company is not held responsible for user-generated content, he explains. But companies still worry about the person who talks about taking a drug and relaying all of the adverse events that started happening. You are limited in how you can respond, he explains. "Short of saying, 'We're very sorry that you had this experience; please call our drug-safety department for follow-up,' you can't really say very much."

Still, negative comments about a drug on a pharma social media site may have less bite than do negative reviews for other consumer goods. Patients are savvier and recognize that individual experiences will vary on a drug. Wasserstein notes, "Patients also have their doctors who are discussing things with them and explaining the likelihood of adverse events." While a bad comment could cause some concern, it's unlikely to tarnish the reputation of a pharmaceutical company.

FDA TO PROVIDE LONG-AWAITED GUIDANCE

On another front, pharmaceutical companies also appear to be avoiding FDA enforcement actions in their use of social media. Last year, the FDA issued only 10 warning letters for promotional violations, down from 24 in 2013 and 50 in 2010. Nevertheless, three of the FDA actions last year were for electronic promotions, including those on Google-sponsored links and Facebook.

Still, Wasserstein says the FDA is focused more on developing social media guidance than trying to announce or clarify rules through enforcement.

The FDA last summer issued long-awaited guidance on using limited space posts, such as the 140 characters on Twitter and Google-sponsored links, for drug promotions. The FDA still requires drugmakers to present a balance of risk and benefit information in these posts, something that is virtually impossible to do to in a short tweet, industry complained. More helpful, the FDA last summer issued guidance that says companies do not have an obligation to correct misinformation created by third parties on their sites.

Drugmakers appear to be avoiding promotional rules in social media altogether by focusing on unbranded disease states, such as the meningitis site. "They're giving patients a chance to interact and understand that there are options out there, without necessarily saying what the options are," Wasserstein says. "In other words, they're trying to increase the pool of participants without necessarily pushing a particular promotional message."

Such efforts demonstrate that a company is a responsible participant in the community. "You talk to any of the social media gurus, and it's all about community building, not pushing messages about a drug," Wasserstein says. "You lose a lot of credibility if that's what you're doing." At the same time, participants understand that in the background there is a drug company and there are solutions without necessarily talking about the drug.

IMS's Aitken underscores the value pharma companies also get when hearing directly from patients about their healthcare experiences and their views on alternative treatment options, especially if the individuals may benefit from the company's products. "They are able to capture 'raw' comments from patients that are otherwise expensive or difficult to obtain," he says. "The directness of the communication is unique and removes intermediaries such as payers and providers, though their role is still critical."

SOCIAL MEDIA CONTINUES GROWTH, ESPECIALLY AMONG OLDER ADULTS

Aitken also points to another driving value factor in pharma's growing interest in social media: the sheer number and range of sites along with increasing consumer participation. This point is born out in a January 2015 report from the Pew Research Center that finds 71 percent of all U.S. adults last year followed Facebook, up from 67 percent in 2012. Other popular social media sites have much lower penetration rates but have seen membership jump even more. Twitter, for example, had a 23 percent follow rate last year, up from 16 percent in 2012, according to Pew.

Furthermore, online users have been skewing toward people more likely to use drugs. Roughly 56 percent of Internet users ages 65 years and older used Facebook last year, up from 45 percent who did so in late 2013 and just 35 percent who did so in late 2012, according to Pew. This is an exciting space for pharma companies, Aitken says. "Not only because of the way in which social media is used every day by millions of consumers and patients, but also because its growing use is happening at the same time other changes are afoot in our healthcare system."

Some of those consumer-shifting changes include a move to high-deductible plans, the vast pool of newly insured individuals via the new health insurance exchanges, or Medicaid expansion and the greater focus by payers and providers on patient outcomes and performance of the health system.

WEIGHING THE COSTS AND BENEFITS

But that doesn't mean drugmakers should jump into social media without a serious cost-benefit analysis. "There are a lot of costs," Wasserstein says. "You're going to need personnel dedicated to monitoring. You're going to need extensive discussions about what kind of messaging you're going to craft that go well beyond what your traditional promotion review looks like. You have to be careful because your messaging is being put out there to a much broader audience than you typically see for a promotional piece."

And chatting directly with individuals raises a whole host of concerns, particularly that the company is not overstepping the bounds between a doctor-patient relationship by dispensing medical advice, but rather playing a supportive, adjunctive role, he says. "It's a very tough balance," Wasserstein notes. "The companies that have done it have found it very rewarding, but from a regulatory and legal standpoint, you have to be very careful."

Liquid Courage – Evaluating Insider Liquidity

ROBERT BIGGS & JACOB GUZMAN

When we meet with CEOs of emerging growth companies, there are two main concerns that keep them up at night: raising money and best positioning their business to maximize shareholder value. Most CEOs understand that their molecule is either going to work or not work; after all, biotech is a binary business.

However, it is their job to shepherd their asset through the necessary pathways in order to maximize value for investors. Since the IPO window opened for biotechnology companies, we have had a number of wealth management clients who are executives of biotechnology companies jump headfirst into the public markets. The hope is that they will be able to utilize the capital markets to raise subsequent money for their company while providing liquidity for current shareholders. In a perfect world, these are both possibilities, but, as we all know, the market is far from perfect.

From an outsider's perspective, some of the key advantages of having a publicly traded company are liquidity and access to capital markets. However, as many senior executives of recently public healthcare companies have found, a successful offering does not always translate into personal liquidity. As you consider your personal liquidity, there are a number of factors to consider including, but not limited to, trading volume and overall market optics.

ASSESSING YOUR PERSONAL LIQUIDITY

Most importantly, as an executive of a newly public company, there are a number of rules and regulations you must follow in order to gain liquidity from your equity position. We have been able to help our clients diversify away from their large single-stock positions in a variety of ways such as a Rule 144 sale of stock (i.e., the public resale of restricted or control securities if a number of conditions are met including holding period, current public information, trading volume, and filing of a form 144), exchange funds (i.e., transferring company stock into a diversified, actively managed pool of assets), collateralized loans (i.e., borrowing against your company stock), and 10b5-1 trading plans (i.e., entering into an agreement during an open window to sell stock with predetermined parameters over a set time period in the future). Given the often fluid nature of trading windows for healthcare companies, and biotech in particular, a popular strategy for liquidity is the 10b5-1 trading plan. Such a selling plan allows you to set the parameters (i.e., price, amount, time frame) for the sale of your stock at a future point in time in order to avoid potential blackouts and periods in which possession of nonpublic material information may prevent the sale of stock. Through disclosure on both Form 4 and 144, a 10b5-1 trading plan can help to mitigate negative signaling issues associated with your intentions to sell in the future. If implemented properly, a 10b5-1 trading plan also provides an affirmative defense against insider trading claims.

“There are a number of rules and regulations you must follow in order to gain liquidity from your equity position.”

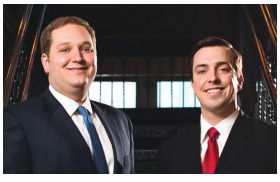
The feedback that we have received from seasoned biotechnology entrepreneurs of newly public companies is that the market is more receptive to preset trading plans today than ever before. However, it is clearly on a company-by-company basis. Given volume restrictions, as well as overall optics, some executives end up with only slightly more liquidity than they had before the IPO.

CONSIDERING THE PERSONAL IMPACT OF GOING PUBLIC

As you consider the personal impact of an IPO, one question to ask yourself is, “What do we really want to get out of this IPO?” From a diversification perspective, what is your ideal level of exposure relative to your overall liquidity profile? Being thoughtful and deliberate in the handling of your equity position can make a significant difference for you and for the overall performance of your company’s stock.

If you do decide to sell, the next decision is how to go about doing so. Are you going to sell in a block, or will you use a 10b5-1 plan? When evaluating your plan for personal liquidity, it is important to consider how you own your shares as well as the different nuances between incentive stock options, nonqualified stock options, and restricted stock. Determine the personal tax ramifications of a sale of stock or the exercising of options. There are various strategies that can be implemented to help make your eventual stock sale as tax-efficient as possible. Even during the post-IPO lockup and blackout windows, you can put the appropriate pieces in place to execute your selling strategy once your window opens.

Two key factors in this whole process will be the volume of your stock and the optics around your sale of stock. As a senior executive, you will be subject to sale quantity limitations relative to your company-stock trading volume. This may prevent you from selling the amount of stock that you would like in the period of time you prefer. Another important factor is that, as an executive, you are required to file a Form 4 with the SEC to identify any change in beneficial ownership (regardless of whether the trade is part of a 10b5-1 plan or an open window transaction). There have been a number of scenarios in which executives have found that it was more beneficial to the long-term value of the company’s stock to hold their shares. L



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How BARDA Is Helping Speed Up Drug Development/Manufacture

CATHY YARBROUGH Contributing Writer @sciencematter

An unusual federal government agency, the Biomedical Advanced Research and Development Authority (BARDA), is providing funding and technical expertise to more than 85 pharmaceutical and biotech companies and 25 academic organizations.

The goal is to accelerate the late-stage development and manufacture of vaccines, drugs, diagnostics, and medical devices that could prove vital to protecting public health during an anthrax outbreak, a bioterrorist nuclear event, pandemic H7N9 (avian flu) epidemic, or an emerging infectious disease that is antibiotic-resistant.

Since opening its offices at the U.S. Department of Health and Human Services (HHS) in 2007, BARDA has supported the development and the manufacture or purchase of more than 160 vaccines and therapeutics. BARDA refers to the products in its portfolio as medical countermeasures (MCMs).

The agency has supplied the federal government's Strategic National Stockpile with more than 10 novel MCMs, including anthrax and botulinum antitoxins, which were licensed by the FDA under the Animal Efficacy Rule. In addition to MCMs for smallpox, anthrax, botulism, and pandemic influenza, BARDA's portfolio includes vaccines and drugs for other viral hemorrhagic diseases such as Ebola and Marburg.

"Overall, the FDA has approved more than 20 BARDA-supported MCMs, mostly for pandemic influenza. Eight of these MCMs were approved by the FDA in the last three years," explained Robin Robinson, Ph.D., director of BARDA and deputy assistant secretary for preparedness & response at HHS.

BARDA, with a 2014-2015 budget totaling more than $2 billion, helps underwrite the advanced development and production of therapies for injuries resulting from chemical, biological, radiological, and nuclear (CBRN) accidents and bioterrorist attacks. The design, development, manufacture, clinical testing, and stockpiling of pandemic H5N1 and H7N9 vaccines and a new class of broad-spectrum antimicrobial drugs against multidrug-resistant "superbugs" also are supported by the agency. BARDA was created by the Pandemic and All-Hazards Preparedness Act of Congress in 2006 to help safeguard the U.S. population from deadly human-made and naturally occurring threats that are not widely addressed by industry.

"Companies have little commercial incentive to invest in a therapeutic against a potential threat that we all hope will never happen," said Moncef Slaoui, Ph.D., chairman of vaccines at GSK, which has developed and manufactured three FDA-approved products with BARDA's support (Raxibacumab, a human monoclonal antibody for preventing and treating inhaled anthrax; the Q-Pan H5N1 influenza vaccine; and the antiviral drug Relenza). BARDA has provided similar assistance to GSK for the late-stage development and manufacture of the Ebola vaccine that the company developed with the NIH and that is now under evaluation in Phase 3 clinical trials in West Africa.

Dr. Slaoui pointed out that BARDA's funding does much more than enable pharmaceutical and biotech companies to design and produce MCMs. The agency's support allows companies to "maintain and sustain the scientific know-how and expertise that could be required one day to discover drugs for an emerging infectious disease," he said. "Someday, we don't know when, a bacterial infection that's highly resistant to available antibiotics could emerge." The resistant microbe could be a product of nature or a bioterrorist's lab.

MCMs developed and manufactured with BARDA's support are purchased by HHS for the national stockpile. BARDA does not prohibit partner companies from marketing MCMs outside the U.S., Dr. Robinson said. However, except for flu vaccines and antivirals, MCMs are not in great demand, he added.

DESIGNED TO ACT LIKE A PHARMA COMPANY

Because BARDA works primarily with industry, Dr. Robinson said that the agency was designed to act more like a pharmaceutical company than a government office. In fact, when explaining the agency's approach to funding, he referred to making investments in companies, product portfolios, deliverables, and milestone payments — terminology more often associated with a VC firm executive, not a government official.

So that BARDA and its corporate partners can speak the same language, the agency's senior positions are staffed with veterans of the FDA and the pharmaceutical and biotechnology industry. For example, Dr. Robinson was director of vaccines at Novavax, Inc. prior to joining HHS.

"BARDA is similar to a VC firm in that the agency invests in late-stage, high-potential programs and promising product candidates. However, BARDA does not take equity in the product," said Adam Havey, executive VP and president, biodefense division, at Gaithersburg, MD-based Emergent BioSolutions, which developed and manufactures the BioThrax anthrax vaccine with funding from BARDA totaling $660 million.

Dr. Slaoui added that BARDA, unlike a VC, does not measure its ROI by financial returns but by its level of preparedness for a public health emergency. No other country's government has an agency like BARDA, he said.

BARDA's portfolio of MCMs targeting Ebola includes ZMapp, the experimental drug cocktail of three monoclonal antibodies that came to the world's attention in August 2014 when several health workers in Liberia and the U.S. became infected with the deadly virus and were treated with the drug under the FDA's compassionate use program. ZMapp's monoclonal antibodies are produced in a time-consuming process in tobacco plants at Kentucky Bioprocessing. In September 2014, ZMapp's developer, Mapp BioPharmaceutical, signed a multi-year contract with BARDA with a base value of $24.9 million to support late-stage development and manufacturing of the drug cocktail. In early March 2015, clinical trials of ZMapp began in Liberia. If ZMapp proves safe and effective in clinical trials, hundreds of doses of the drug could be manufactured for wide distribution by the end of 2015.

In addition to providing funding, BARDA has helped Mapp BioPharmaceutical, headquartered in San Diego, improve its processes for purifying the monoclonal antibodies in the cocktail and arranging for Nanotherapeutics/Baxter, a member of the agency's fill-finish manufacturing network, to deposit ZMapp into vials. The network is one of the BARDA's core assistant services for the recipients of agency funding and technical support.

Mapp Biopharmaceutical President

Larry Zeitlin, Ph.D., said, "BARDA has provided us with access to their manufacturing and regulatory subject matter experts and has been involved along with the NIH and FDA in the design of clinical trials," he added. "BARDA has been an important and responsive partner."

MAKING IT ACROSS THE FINISH LINE

Many of BARDA's industry partners are small biotech companies like Mapp Biopharmaceutical that do not have extensive experience with clinical trials, regulatory submissions, and manufacturing and packaging. BARDA's core assistance services are designed to help these small companies "make it across the finish line to FDA approval," said Dr. Robinson.

"BARDA has an excellent track record at partnering with companies to develop drugs and bring them to licensure," said Dr. Zeitlin.

"BARDA truly tries to help contractors succeed," added Havey.

In addition to its fill-finishing network of five CMOs, BARDA's core services include a national network of 17 companies with expertise in lab animal studies, clinical studies network of five CROs, and three Centers for Innovation in Advanced Development and Manufacturing (CIADM).

CIADMs, the centerpiece core service, provide the U.S. with the "nimble and flexible" domestic infrastructure needed to manufacture MCMs under a tight deadline, said Dr. Robinson. By using 21st century technologies, he said, CIADMs can produce 50 million doses of a pandemic flu vaccine within four months of an outbreak. The centers also are required to manufacture vaccines or biologics for public health emergencies such as Ebola and provide workforce training and core services to support the development and production of CBRN MCMs. Each CIADM is a partnership between an academic institution and a pharmaceutical or biotechnology company.

GSK and Texas A&M University System are partners in the $131 million Texas CIADM vaccine manufacturing facility. BARDA's funding for the facility totals $75 million. When completed, the Texas CIADM will provide GSK with its only U.S.-based facility for developing and manufacturing its pandemic and seasonal flu vaccines. Other current GSK projects with BARDA include developing cell culture-based influenza vaccines for seasonal and pandemic flu, H1N1 vaccine, as well as adjuvanted pandemic influenza vaccines against H7N1, H9N1, and H5N1 influenza. Production of broad-spectrum antibiotics against "superbugs" also is on GSK's list of BARDA projects, which are supported by $700 million in agency funding.

Like GSK, Emergent BioSolutions has been a BARDA partner since 2007. BARDA funding enables Emergent to manage the agency's CIADM in Maryland and manufacture millions of doses of BioThrax for the nation's stockpile. When the company's new Lansing, MI manufacturing facility is approved by the FDA, Emergent should be able to boost its annual BioThrax production to 20 to 25 million doses from the 7 to 9 million doses now being manufactured. BARDA also is funding Emergent's evaluation of BioThrax's effectiveness as a postexposure prophylaxis, as well as three new experimental anthrax products under development at the company.

TIPS FOR EFFECTIVE PARTNERSHIP

Dr. Slaoui of GSK and Havey of Emergent BioSolutions said that the ingredients of an effective partnership with BARDA are:

- "... respect, characterized by active listening, engagement, and participation." — **Dr. Slaoui**
- "... joint decision making based on data rather than opinion or belief. BARDA and its industry partner together should analyze and interpret data." — **Dr. Slaoui**
- "... very frequent and open interactions." — **Dr. Slaoui**
- "... achieving BARDA's expectations about deliverables." — **Dr. Slaoui**
- "... technical expertise required to deliver results. Take advantage of BARDA's clear guidelines on processes that can be integrated into a product development plan." — **Havey**
- "... transparency in communications. We often receive valuable advice from the agency. The nature of development programs is to have unexpected or unpredictable results, and regardless of outcome, timely and open communications with BARDA could reduce unnecessary delays."— **Havey**

"The FDA has approved more than 20 BARDA-supported MCMs [medical countermeasures], mostly for pandemic influenza."

ROBIN ROBINSON, PH.D.
Director of BARDA and deputy assistant secretary for preparedness & response at HHS

Havey added, "Typically, the U.S. government requests more than one round of technical and business questions and/or proposal/application revisions prior to award. Companies must ensure that all required supporting documentation is ready for submission and must have an in-depth understanding of the technical and business terms of the contract or grant."

As the H1NI flu pandemic of 2009, the H7N9 outbreak of 2013, and the Ebola epidemic of 2014 and 2015 have shown, cancer, cardiovascular diseases, diabetes, and Alzheimer's disease are not the only health threats to the U.S. population.

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Building A Patient Advocacy, Diversity, And Engagement Focus At BMS

ED MISETA Executive Editor, Outsourced Pharma @OutsourcedPharm

When Lori Abrams was named director of advocacy, diversity, and patient engagement for Global Development Operations at Bristol-Myers Squibb (BMS), she had no one to manage. In fact, her first assignment was to create the department she would oversee. "The first thing I realized was there didn't seem to be many such departments for me to benchmark against," she notes. "I went around to a lot of pharma companies trying to find someone to talk to, but an advocacy position focused on clinical trials just didn't seem to exist."

Undeterred, Abrams set about building the department the way it would best serve patients. She was able to pull from her experience working as a patient advocate (and common sense), and she used a lot of trial and error along the way. She also engaged with patient advocacy groups, asking a lot of questions about how pharmaceutical trials could best meet the needs of patients. With three employees now on her team (and two on a work rotation) overseeing all patient aspects of drug development for all therapeutics, it's safe to say she has come a long way.

"The Advocacy, Diversity, and Patient Engagement Group collaborates with disease-based and minority-focused advocacy organizations as early as Phase 1 to learn about the patients and caregiver's daily challenges as well as their concerns about clinical trial participation. The group also meets to understand what secondary endpoints may be important for the patient. By connecting with patients and advocacy organizations, we are also able to drive recruitment, educate patients on current studies, identify participation barriers, understand the special needs of the patient population, and identify study sites and investigators."

A key aspect of her job is bringing awareness and accessibility of clinical trials to patients, hopefully leading to increases in enrollment. To that end, understanding the journey of a patient is vital. For example, how many visits did they have to make? How invasive were the tests? How many times did the clinic have to draw blood? She believes the relationships nurtured through advocacy can help companies get the answers they need to understand the priorities of those affected by the disease. She believes these answers will also help pharma and bio companies improve their understanding of investigational therapies across broad and diverse populations.

CHALLENGES TO OVERCOME

From her first day, Abrams knew a key component of her new job would be to design and deliver a clinical trials advocacy team that would remove or minimize barriers that prevented greater participation in clinical trials. To be successful, that team would have to collaborate across the BMS enterprise, including operations, research, medical, legal, regulatory, market access, and other departments to ensure the strategies she put in place were understood and synergistic with other business goals and objectives.

"As a former protocol manager, I knew that changes to company culture, specifically those that may bring new sites or recruitment tactics, would be a challenge," she says. "I think that was probably my biggest concern coming into the position. At the same time, I felt I was building a team with the capacity and credibility to apply and translate patient, caregiver, and competitive insights, in order to effect change that would make our trials more appealing."

One of the biggest challenges Abrams faced took her well over a year to identify. It was the notion that some disease-focused and minority-focused advocacy organizations could not deliver everything they promised or what her company desired. Thus, she says it's important to quickly identify the strengths of a patient advocacy group (PAG). "Once you fully understand those strengths, you only ask them to do what you know they are equipped to succeed at," she says. "If there is something you know they are not equipped to do, find another organization to perform the task."

She also stressed the importance of

maintaining those PAG relationships. "When you give your word to patients, it's important to keep it, even if it is not the popular thing to do. Building trust and credibility with these organizations can be a challenge. If there is distrust that exists right from the start, relationships are incredibly more difficult. While this challenge can be overcome given enough conversations, they can take a long time, depending on the PAG."

DEFINE SUCCESS EARLY

Projects often fail simply because key decision makers don't identify the characteristics of success for the endeavor. Abrams took the time early in the process to define what success in her position would look like. First, she wanted to have a seat at the decision-making table at every appropriate step in the trial development and execution process. Today, consistently getting that invite is one measure of success for her group.

Second, there are metrics she can monitor to measure aspects of trial success from her perspective. How many ethnic minority physicians who are new to BMS have become investigators in the last six months? Have her advocacy tactics allowed the company to reach a more diverse patient population? If so, how does randomization look? And most importantly, have PAG insights helped to improve protocol designs? These are all areas that Abrams attempts to monitor and better understand.

"To be successful in this role, I also learned early on to embrace change, seek innovation, and take risks when necessary," she notes. "Quick wins in the beginning, supported by data and/or early adopters, also helped to bring the department needed credibility. The early development of an advocacy guidance document in collaboration with our legal department was also critical. In addition to providing clear definitions of what our group could and could not do, it delineated the differences between clinical trials advocacy, medical advocacy, and commercial advocacy."

Finally, Abrams notes advocacy, diversity, and patient engagement encompass an enormous body of work. Therefore, be careful not to try and accomplish everything at once. She recommends establishing objectives, prioritizing them, and sticking to the plan. When doing so, be sure to maintain flexibility as business priorities shift.

PROPERLY ENGAGE WITH PATIENT ADVOCACY GROUPS

For many individuals, engaging with patient advocacy groups might be considered one of the most difficult aspects of the job. For Abrams, the work she did with these groups in the past (see sidebar on next page) prepared her well for the role. "This is probably the easiest component of my job," she says. "There are several

From Patient Activist To Director of Advocacy

Lori Abrams did not begin her career in Big Pharma by going the conventional route. She does not have a degree in biology, chemistry, or engineering. In fact, when she started her career in the life sciences industry she did not have a degree, and science would not have been her first choice of major. But when a couple of close friends contracted the HIV virus, she decided to become part of the effort to find a cure.

That drive led her to take a job at NIH where she served as study coordinator. She then worked for the Henry M. Jackson Foundation as senior protocol coordinator, managing HIV/AIDS clinical trials for the military. By 1998 she was managing multiple global Phase 3 clinical trials on HIV/AIDS compounds for Bristol-Myers Squibb (BMS), later becoming an associate director in the R&D learning department. Along the way she obtained a B.S. degree in health science, a master's certificate in organizational development, and completed several BMS leadership programs.

"At the end of 2011, someone recommended I apply for a new position the company was creating to oversee advocacy, patient engagement, and diversity in the clinical trial space," she says. "I felt this was the role that would allow me to truly make a difference in the lives of patients. I applied for the job not even fully aware of what exactly it would entail. When the company became aware of my role as a patient advocate and activist in Washington, D.C., I was quickly offered the position."

methods for identifying the appropriate disease-focused and minority-focused advocacy groups. Once we have developed our strategic plan, we can reach out to the organizations we have not worked with in the past. Generally a preliminary call is made where we identify the goals of the PAG and loosely discuss ours. If there are synergies, we move ahead and begin to build a relationship."

First BMS will identify patient advocacy groups applicable to a study, collect information on the groups from peers, and narrow the list down to the top prospects. Abrams will then conduct preliminary calls to determine if the objectives of BMS and the PAG align, understand their focus (i.e., education, clinical research, policy), whether they have the experience and bandwidth to collaborate, and their track record of collaborating with pharma.

Abrams often advises colleagues that, when working with PAGs, the "devil is in the details." While everyone agrees it is important to engage patients throughout the process of drug development, how that patient engagement is designed into day-to-day operations is not always clear. Advocacy campaigns can drive awareness of a clinical study, but there are many steps that fall between awareness and enrollment.

"Campaigns should be designed to help us generate data that will illuminate the many steps of our patients' journeys, so we can document how and where their engagement makes a difference," says Abrams. "Initially this effort might only make a difference to one patient, but we have to look at the bigger picture and understand that ultimately it will make a difference for all of the patients that follow. The pharmaceutical industry is analytical, data-driven, and objective. It has to be. But the patient experience is physical, emotional, and personal. It is the role of the patient advocacy department to bridge these two worlds in order to bring medicines to market that have a demonstrable benefit to patients from all walks of life."

HIRE THE RIGHT DIRECTOR

Any company starting a clinical trial patient advocacy department wants it to get off the ground smoothly and efficiently. But what kind of person should pharma companies look for when hiring a director of patient advocacy? And what skills and background should that person possess?

While a strong understanding of business and specifically drug development is a good background to have, Abrams notes the first trait she would look for is someone who can build relationships based on trust, mutual respect, empathy, and understanding the business from the perspective of the patient and caregiver. These are critical traits, and she believes savvy external stakeholders can quickly assess the authenticity of such a person.

"The individual needs to have the ability to work across an enterprise and break down boundaries," she notes. "A good portion of my job is problem solving, building alliances, and bringing about meaningful outcomes. If you are not empathetic to that patient point of view, this is a very difficult thing to do."

Taking risks and trying new ideas and new tactics is also critical, especially as the patient environment continues to change and patients become more informed about clinical trials and the drug discovery process. "I need to have the self-confidence to fail, but get right back up to fight another day," she adds. "In that regard, having the support of management is also very important. Without that support, many of my efforts would be futile."

While there is no typical day in her position, Abrams does spend a good amount of time focusing on:

- internal stakeholder management
- advocacy team/issues
- external relationships (managing existing relationships and building new ones)
- participation in external advocacy and/or diversity work streams
- innovative brainstorming with multiple stakeholder groups
- keeping up with the BMS book of work/business goals.

Team members spend most of their time developing strategies and tactics to engage patients in protocols, developing communications for advocacy organizations, refining relationships, and reviewing and modifying study materials to be more patient-friendly.

Adds Abrams, "Ultimately, we need to be able to look back and ask if we did everything we could to make patients aware of our trials and make those trials as user-friendly as possible. Our focus must be on the patient. Only by having that mindset will we be able to function in this role and meet the goals we have set for ourselves. It can be difficult at times, but we have the benefit of knowing that everything we do will make a difference in the life of a patient. And that has been my goal since I started at the NIH."

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At Navidea, A Scientific Advisory Board Points To New Directions

LOUIS GARGUILO Executive Editor @Louis_Garguilo

Until recently, Navidea Biopharmaceuticals (NYSE: NAVB) described itself as a leader in precision diagnostics that identify the presence and status of diseases. It focused on the development and commercialization of precision diagnostic agents for conditions such as cancer, dementia, and movement disorders.

That was then. Ricardo J. (Rick) Gonzalez, president and CEO of Navidea, doesn't plan to stay put. Which turns the company makes along the way to new business strategies will be decided in large part with direction from the Scientific Advisory Board (SAB) Gonzalez is currently assembling.

"There's an evolution going on at Navidea," says Gonzalez. "A big part is our growth out from a diagnostic focus into considerations of the therapeutic space. This can be a long road that offers great opportunities, but comes with embedded challenges. To manage this, we have the philosophy of questioning everything with the intention of optimizing what exists and continuing to drive into the future."

Gonzalez will task his SAB with simultaneously providing and challenging the map to new business models. The good news is his board will have a relatively advanced starting point. Navidea, founded as Neoprobe Corp. in 1983, has gained a solid market footing with the product Lymphoseek (technetium Tc 99m tilmanocept injection) — a receptor-targeted, radiopharmaceutical imaging agent — approved by the FDA in 2013 and the EU in 2014. Navidea just announced on March 5 that it entered into an exclusive sublicense agreement for the commercialization and distribution of Lymphoseek in the EU, with SpePharm AG (an affiliate of Norgine BV). Navidea also has two imaging agents in Phase 3 development, NAV4694 (Alzheimer's disease), and NAV5001 (Parkinson's disease), as well as a handful of Phase 2 trials.

So, is this optimal timing for Navidea to form an SAB?

THE WHENS AND WHYS OF SABs

SABs are not new, novel, or a sure bet for enhancing progress or success, no matter what the company stage. Bruce Booth, writing for *Forbes* back in 2012, said, "Almost every biotech has a Scientific Advisory Board, but few use them particularly well. Although SABs can be hugely valuable ... they can also be a colossal distraction and huge time sink." He went on to say SABs aren't free, and especially larger ones have a high degree of entropy. Various opinions from highly skilled professionals and scientists "can lead to a herding of cats during meetings," according to Booth.

Fair warnings, for sure. However, SABs have been around and studied now for decades; lessons certainly have been learned. In fact, Gonzalez can benefit from knowledge gained from a scientific advisory board established at Macrophage Therapeutics, a subsidiary of Navidea. This SAB was established specifically "to develop therapeutic applications for the Manocept platform, the technology upon which the company was formed." The board is composed of scientists and clinicians in the areas of oncology, immunology, autoimmune diseases, and macrophage biology.

It's also worth mentioning here that historically SABs grew in importance due in part to unintended consequences of the Sarbanes-Oxley act of 2002. Sarbanes-Oxley forced corporate boards to focus on financials and matters of compensation and legal disclosure. Even for relatively smaller biopharma companies like Navidea (currently 40 employees), because of the potential for broad application of fast-changing and complex science and technology, there's little time for corporate boards to focus substantially on future planning.

Another salient point is that for pre-IPO and early-stage organizations, SABs play the role of company — and technology — validators. When companies become more established, SABs are then a support system for internal scientific management and product development. They also provide the time-constrained corporate board with a valuable link to prog-

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ress in these areas.

Which brings us back specifically to Navidea and CEO Gonzalez.

ADVISING ON THE UNIQUE

"The genesis of the Navidea SAB is predicated on the unique ability of our technologies to target cells that could not be targeted before," explains Gonzalez. He adds, "So that's the broad statement." Now Navidea needs to understand how to yield value.

"The SAB is where we mine the company data, where technology meets scientific and clinical minds to identify the development path," continues Gonzalez. "For example, when we specifically look at our technology's targeting mechanism to activate macrophages, there are broad applications. Where to put it to best use is the question for the board."

Gonzalez, who works from Navidea headquarters in Dublin, OH, says the company has identified experts around the world with in-depth knowledge of macrophage behavior. They understand the science, but as importantly, they understand the clinical applications and business considerations when advising on next steps.

"The trick is to balance the great minds on the SAB and form consensus. The loudest voice can't win."

RICARDO J. (RICK) GONZALEZ
President and CEO of Navidea Biopharmaceuticals

He first intends to present board members with "the body of evidence that we possess" for discussions on the broad scientific applications. But he wants this done with more of a focus on specific therapeutic areas, the direction Navidea now wants to move in.

One of the potential applications for the Manocept targeting mechanism is in oncology. However, as Gonzalez well knows, oncology is a large field with various opportunities and unmet medical needs. "The question is, then, which scientific advisors become most relevant to that disease state, and then form a working subgroup on how to focus on that therapeutic area," says Gonzalez. "That will be the same with infectious diseases, cardiovascular diseases, and other areas."

THE CEO AND SAB

A difficult first question every CEO needs to answer regarding an SAB, perhaps

most particularly regarding one they have the opportunity to set up: How involved should I be, and what is my role?

Gonzalez has no hesitation in answering. "My background is more commercial, although I've been part of precommercialization and development projects. I won't be directly involved with the scientific aspects of the SAB." He will, though, directly ensure that execution and strategies are in accordance with the overall vision of the company. "I want to facilitate these processes, but I'll rely heavily on others on my staff to lead."

Which forms a second fundamental question: Who takes the reins — or the overall leadership role — on an SAB?

Again, Gonzalez has his answer ready: Michael Goldberg, M.D., a member of the Navidea board of directors since November 2013 and a managing partner of Montaur Capital Partners since January 2007. Dr. Goldberg also has a list of prior positions in biopharma.

With this appointment, Navidea introduces an interesting strategy: Employ an established *corporate* board member and accomplished scientist/business leader to play the role of SAB shepherd. This conveniently covers comments above regarding the role of SABs to keep corporate boards informed of progress and the concerns with getting a group of accomplished members to work together.

Regarding actually managing the SAB, Gonzalez says, "The trick is to balance the great minds on the SAB and form consensus. The loudest voice can't win. Dr. Goldberg and I will set the tone and expectations for the SAB at the get-go to help avoid future issues."

A different issue comes to mind here. An established corporate board member with a leadership role on the SAB could wield too much power. This could potentially stymie proposals expected to have difficulty in getting corporate board approval. For certain, these dual-board roles require a delicate balancing act. Gonzalez has faith in Dr. Goldberg; for his part, he says, "I will be cautious, specifically in our governance approach, and caution the group, in particular, on the management side of the SAB. They must be fully cognizant that we're not here to please a particular group or individual. We're here to accomplish a process as a board." He adds, "Yes, I'll be looking for any potential pitfalls along the way."

Ultimately, says Gonzalez, "Via the SAB, my intention is to answer the 'so-what' question that is vital to companies. You have a technology, you determine a path … what is the value you create? What comes back to us as part of this investment and this process? The focus is on the science and development, but we want to see what's at the end. What are we trying to achieve for our business and our patients? The SAB is a key component of finding our future."

Diversifying Leadership Teams With People Who Have The X-Factor

KARL SIMPSON

Karl Simpson is founder and CEO of Liftstream Limited, an executive search recruitment practice working exclusively in the life sciences sector. He has more than 20 years of experience in the recruitment industry.

Workplace inequality is not a new story, particularly that of gender. During my 20 years of executive recruiting, I've heard almost every conceivable reason why leadership teams remain so distorted in favor of men. Redressing the balance and achieving parity between the genders at the top of organizations is a very long way off in almost any industry you choose to select, best illustrated by the fact that only 3.4 percent of Fortune 500 companies have female CEOs, and women make up just 11 percent of the boards of the world's leading companies. But surely the biotechnology sector, with its strong academic base, is better? Well, the short answer is NO.

The unfortunate reality is that, if today you're an aspiring female executive working in biotech and looking for a place among the C-suite or on the board of a biotechnology company, statistically the odds are very much stacked against you. In fact, among the boardrooms of biotechnology companies ranging from 10 to 1,000 employees, just one in 10 are women, and only four in 100 companies are chaired by women. In the U.S., some 52 percent of biotech companies have all-male boards, and this figure rises to 60 percent in Europe. When the situation is as stark as this, it is little surprise that women point to systemic problems with the way in which leadership teams and boards are selected and configured, a view shared by a growing body of male leaders.

To advocate change, we all need to have data to support our arguments, which here comes in the form of a biotech sector gender study, "Diversifying the Outlook — The X&Y of Biotechnology," and when you analyze the data, it is difficult to ignore the proportional lack of women leaders. To many people, this picture is not a surprise and is confirmation of the problem, whereas other life sciences executives say it merely reflects the real landscape of talent.

For progress to occur, three things need to happen. First, leaders need to accept there is a problem. Second, we need to understand the scale and drivers of it, and then we need to establish an incentive for change. In these few paragraphs, I want to describe today's landscape and provide some positive actions your company can take. Hopefully it will provoke rigorous debates among your board and executive team.

CREATING INCENTIVE

With biotechnology companies resurgent and the recipients of capital inflows, increasing valuations, and healthy investor returns, it is easy to cite these successes and suggest nothing needs changing. The evidence though points toward a clear business case for diverse leadership. Companies whose boards have diversified gender have been shown to outperform those with all-male boards, giving better growth and, on average, high returns on equity with less volatility. So ultimately it is about better business, not fairness as many perceive. After all, men and women share a conviction to a meritocracy and only wish to see the best-qualified employee in place. Leaders commonly agree their leadership team is improved by multiple capabilities and experiences, rigorous discussion and varied perspectives about key decisions, and a more collaborative approach — all hallmarks of a diverse team.

If you are encouraged by this incentive, perhaps enough to add a woman to your board, then think even more boldly. Diversifying your board is going to take audacious courage and sustained effort, as the tokenism of one woman board member is unlikely to have the transformational impact. The research consensus is that for diversified boards to outperform their all-male rivals, they need to achieve a critical mass of women, projected as at least 30 percent — or more than one woman. This is the number at which the board dynamics are sufficiently transformed for the performance returns to occur.

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Whether a publicly listed company or an aspiring private venture, the business case for diversifying your leadership is compelling and the motives varied. One such motive is that you want to be accessing the best talent. So, by neglecting the market of potential women executives, you are insufficiently utilizing the talent pool available to you. Equally, developing good governance strengthens reputation and conveys operational integrity, which attracts partners, investors, and employees, all of which create value.

LEADING POSITIVE CHANGE

Challenging attitudes and mind-sets is vital to improving the diversity picture. Leadership on this topic must come from the top, and chairs, CEOs, and C-suite executives have to begin the transformation. Looking for catalyzing events or windows of opportunity often result in inactivity. Instead, leaders need to start immediately, and with urgency, to introduce corrective behaviors.

Small or midsize companies can tackle this issue too, in spite of their inherent resource constraints. It is commonly suggested there is a correlation between company scale and the need for best-practice hiring and governance procedures. Good leadership is about mastering these issues in the context of your operational culture. There are many examples of start-up and small companies who have shown that with limited resources you can still create a highly diversified team and benefit from their multidisciplined leadership. Scale is no impediment to achieving diversity goals, and it is incumbent upon the chairs and CEO to set the agenda, making it clear that talent is everything, including a diversified team.

Consider also the process by which you appoint people. It is clear that small and growing companies need to be fast, responsive, and agile in recruiting key executives. Sometimes speed is at the cost of quality and can lead to suboptimal selection, although it need not always be so. Hiring people is a big investment, and like other investments, increasing your opportunity for value return is a leader's responsibility.

REACHING OUT BEYOND YOUR NETWORKS

Our research has found that unstructured recruitment processes and an overreliance on personal networks are strong contributors to a lack of diversity, especially in small and midsize companies. Chairs and CEOs need to show clear leadership in the design and implementation of recruitment practices, which will lead to more comprehensive searches for talent and should encompass higher proportions of women on both long and short lists for board and executive positions. When designing those recruitment practices, reject assessment parameters that do not impact job performance criteria. Also, introduce balanced and gender-diverse candidate selection panels as well as transparent decision and feedback mechanisms. In particular, pay attention to interview interaction and internal-decision motives.

Male chairmen and CEOs often talk about their strong desire to recruit women to leadership ranks, but bemoan a deficient pipeline of prospects. Where intent is genuine, the perspective they have toward candidate pipelines is distorted by their own professional networks. This is not to imply that they have intentionally built a network of one gender, but there is every likelihood that through chance and circumstance they will have a gender-dominated professional network. Whenever you begin to think about hiring someone for your team, you think immediately to people that you know, have worked with before, or have some professional connection to. If that mental recall projects very few women, then you're predisposed to assume that the pipeline is short of female candidates.

Where companies have identified this skewed perspective of the pipeline, but have wanted to achieve more balanced representation in their recruiting efforts, conducting more exhaustive searches of the candidate marketplace has garnered qualified people to hire. In a survey we conducted of 530 life sciences executives, where 53 percent of respondents were male and 47 percent female, almost 60 percent of C-level men said they'd been recently contacted about nonexecutive director roles, whereas only 16 percent of the women had. This infers that women are being largely overlooked for these roles, which means your business can find them if it looks and can inherit a competitive advantage in doing so.

> *"If today you're an aspiring female executive working in biotech and looking for a place among the C-suite ... statistically the odds are very much stacked against you."*
>
> **KARL SIMPSON**
> Founder and CEO of Liftstream Limited

EVALUATE WITHOUT BIAS

Eradicating the bias in your company, both conscious and unconscious, is a key milestone toward developing improved equality, while having the effect of improving the way your business functions. Unconscious bias is not about discrimination, as both genders are equally capable of it. We all have these biases which subconsciously influence our views and decisions. The majority of leaders I interview on this topic have not encountered unconscious bias training. However, of the ones who have gone through this training, by turning unconscious biases into conscious ones, they have enabled corrective actions that have considerably improved decision outcomes capable of transforming areas like hiring.

Leaders must engage in this topic; they must be prepared to challenge and to be challenged. It can be a divisive topic fueled by social and political attitudes, but change is needed, and momentum is building. Setting on a path toward team diversity uncovers incredible opportunity, and great people will unlock the potential of your business. Make it your aim. L

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What Big Pharma Can Do To Combat The Latest Patent Cliff

JIM BEDFORD & YVES LECLERC West Monroe Partners

The patent cliff era is far from over for the pharma industry. In the last three years, some of the biggest drugmakers have seen their blockbuster patents expire, a trend that will only increase going forward. A recent study by GlobalData estimates the industry will lose more than $60 billion in revenue through the end of 2019 due to the patent cliff.

Early 2015 analysis from Moody's Investors Service identified Big Pharma players including AZ, Lilly, and Bristol-Myers Squibb as those most vulnerable to patent cliff repercussions, with 30 to 40 percent of their revenues at risk. Over the next two years, these firms alone are predicted to face major patent expirations not just in the U.S., but internationally as well.

Plenty of firms have kept busy building their pipelines and expanding their product portfolios to combat the cliff's inherent risks, but adding products isn't the only solution. In order to stay competitive and maintain healthy margins, Big Pharma leaders need to think more strategically about their supply chains, IT investments, and M&A activity.

SIZE UP SUPPLY CHAIN MANAGEMENT

Operational excellence now has the boardroom's attention. Similar to the challenges historically faced by the consumer packaged goods (CPG) sector, Big Pharma is under pressure to adopt more agile production processes while delivering supreme customer service and product quality. Making good on both demands starts with supply chain evolution.

To keep pace with younger, more nimble generics companies — which usually don't have the legacy overhead or staff to support — firms will need to pivot away from traditional supply chain strategies to a new supply chain network approach. This move requires better demand visibility and end-to-end supply chain integration, not to mention demand and supply collaboration and modernized advance planning and scheduling optimization.

Stronger inventory and plant optimization, higher service levels, and across-the-board cost structure optimization will also be essential to offsetting patent cliff losses. Firms relying on contract manufacturing may need to go to greater lengths to ensure supply chain integrity. As drugmakers pursue new products, they must have full visibility into their suppliers' service quality and potential risks to avoid regulatory noncompliance and minimize damages in the event of a recall.

GO ALL-IN ON IT AND ANALYTICS

Perhaps due to the industry's highly regulated nature, pharmaceutical companies have been slow moving on the technology adoption curve. Many firms have integrated automation capabilities to a degree, but the sector still struggles to shed its "this is how it's always been done" mentality. While the cost of IT change is high, it is time to change.

Established firms should take note from smaller drug start-ups, which consistently create new levels of efficiency by marrying technology and advanced data analytics. From inventory management software to predictive analytics tools, there is a bevy of resources available today that Big Pharma should be using to make more accurate business decisions. Pairing automation with real-time analytics ultimately shortens the new product timeline from R&D to market, expediting the clinical development process and augmenting plant workers' productivity.

M&A CONSIDERATIONS

The patent cliff is a shared struggle throughout the pharmaceutical industry. Given Big Pharma's recent affection for deal making, mergers and acquisitions present another possible solution to sustaining revenue during an otherwise tumultuous time. Firms with products facing expiration may consider acquiring companies rich in biotech development expertise, strengthening their portfolios for a postpatent-cliff era.

On one side, M&A provides another avenue for diversifying drug portfolios and getting access to new, promising molecules. Conversely, some firms may look into divestiture activity to shed nonrevenue-generating divisions and minimize operating costs. Potential acquirers and hopeful targets should stay current on deal trends to take advantage of these collaborative opportunities.

The patent cliff isn't a terminal diagnosis for the pharmaceutical industry, but rather an inevitable growing pain. With the number of options at its disposal, Big Pharma should be able to clear this hurdle unscathed — so long as they start planning and executing new operations and technology approaches now. L

Jim Bedford is a director at business and technology consulting firm West Monroe Partners in Chicago.

Yves Leclerc is a managing director at West Monroe Partners.

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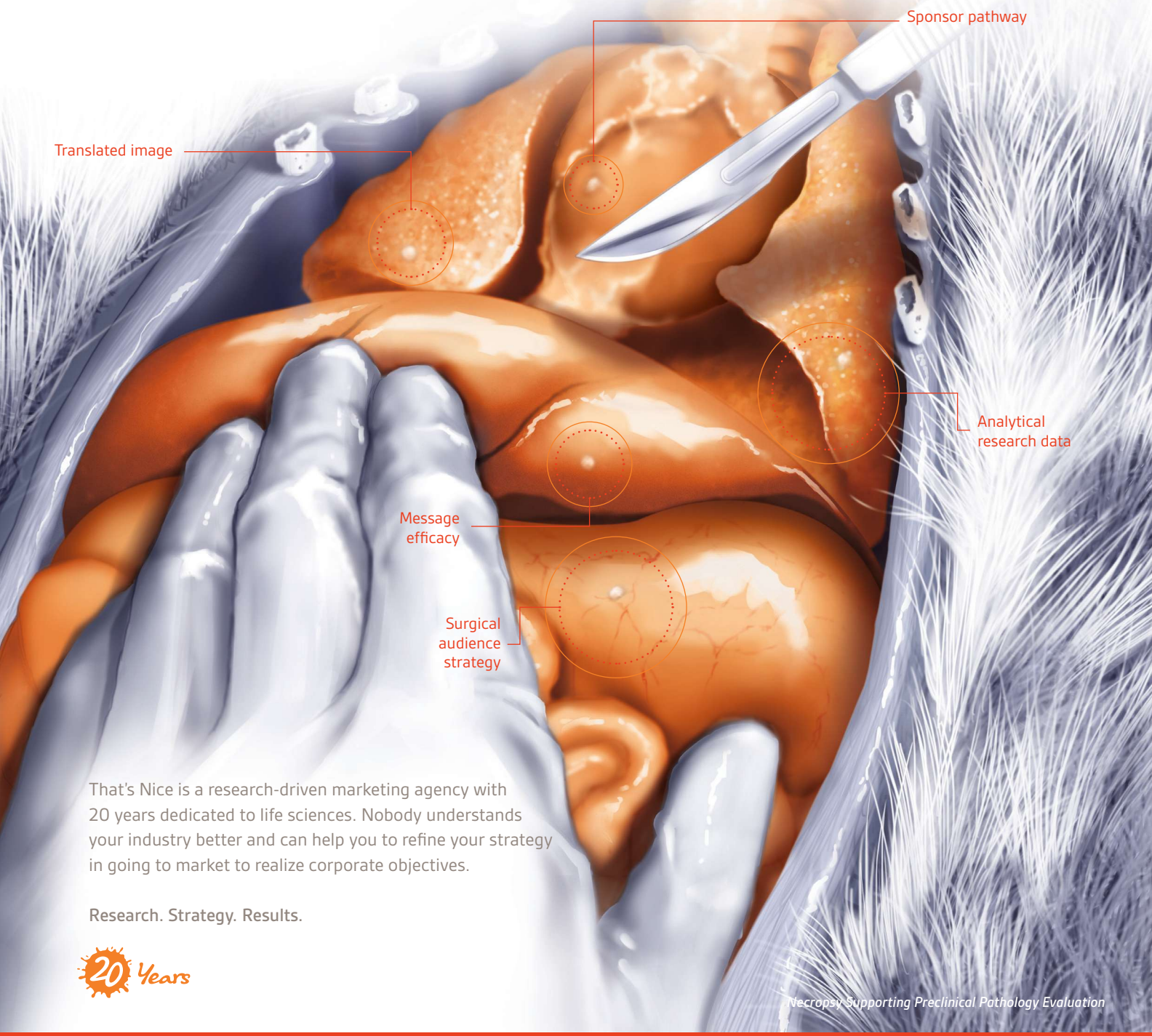

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Hiring Right Might Save Your Job

ROXI BAHAR HEWERTSON

How often have you hired the wrong person for the wrong job? If you regularly hire people, you're likely to have missed far more than once. Painful, isn't it? But you are not alone.

FACT 1

Nationally, about 50 percent of hires fail. Of those that succeed, only about 20 percent are top performers.

FACT 2

Ninety percent of failures are *unrelated* to technical skills.

FACT 3

The cost of a bad hire is up to two times the person's annual salary and benefits ... until you fire them or they leave. How much you lose depends on how awful they are and how much time, money, and productivity is flushed away in the meantime. Then, add another two times to two and a half times their salary costs to replace them.

FACT 4

Turnover in any position costs you real money. Turnover of good people leaving because they don't want to work with your bad hires costs you even more.

None of this is good news for you, the hiring supervisor or leader. And none of this is theory; these are all well-researched facts. And yet, we hire most people and positions based on their shiny new (or old) degrees and/or technical skills along with perceived or tested IQ. We now know, for a fact, that EQ (emotional quotient/intelligence) is far more important for success in most jobs and definitely within leadership roles. Yet, incredibly, we continue to hire and promote people, including leaders, largely for IQ and technical skill sets. "The best scientist will surely be the best leader of other scientists." Right? WRONG!

Leadership authority Roxi Bahar Hewertson, CEO of Highland Consulting Group, Inc. and AskRoxi.com, brings over three decades of practical experience in the worlds of business, higher education, and nonprofits. She is an entrepreneur, consultant, speaker, and author of the book *Lead Like it Matters ... Because it Does.*

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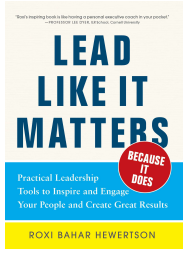

It just gets dumber and dumber. We keep getting the same lousy results, and yet we have not fundamentally changed the ineffective hiring practices in most organizations. It is mind-boggling! I believe Albert Einstein had something clever to say about this phenomenon being related to insanity.

Whatever methods (legal and ethical, of course) you use, you need to discover at least these six key things about your candidates before you hire.

- **A ATTITUDE:** Is it one of abundance and can-do, or scarcity and focused on obstacles?
- **B BRAINS:** Can they do the job or learn quickly how to do the job?
- **C CHARACTER:** What are their core personal values?
- **D DRIVE:** Are they self-motivated to achieve their goals and yours?
- **E EXPERIENCE:** What have they done in the past that prepares them or makes them ready for what you want them to do now?
- **F FIT:** Will they truly fit into your culture and your organizational values and help you accomplish your mission and advance your vision?

If you said "no" or "can't tell" to even one of these six questions about the candidate, do *not* hire that person.

Trust the answers to ABCDE and F, and trust your gut. If the person doesn't feel right to you or others, they probably aren't right. In any case, it's rarely, if ever, worth the risk to you and your team.

Hiring right is an art and a science. Smart leaders make the time to take the time needed for learning about and understanding the human being they are inviting into their organization. New hires change the dynamics, impact morale, productivity, and the bottom line, so it surely ought to matter to the leaders to get it right! L

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