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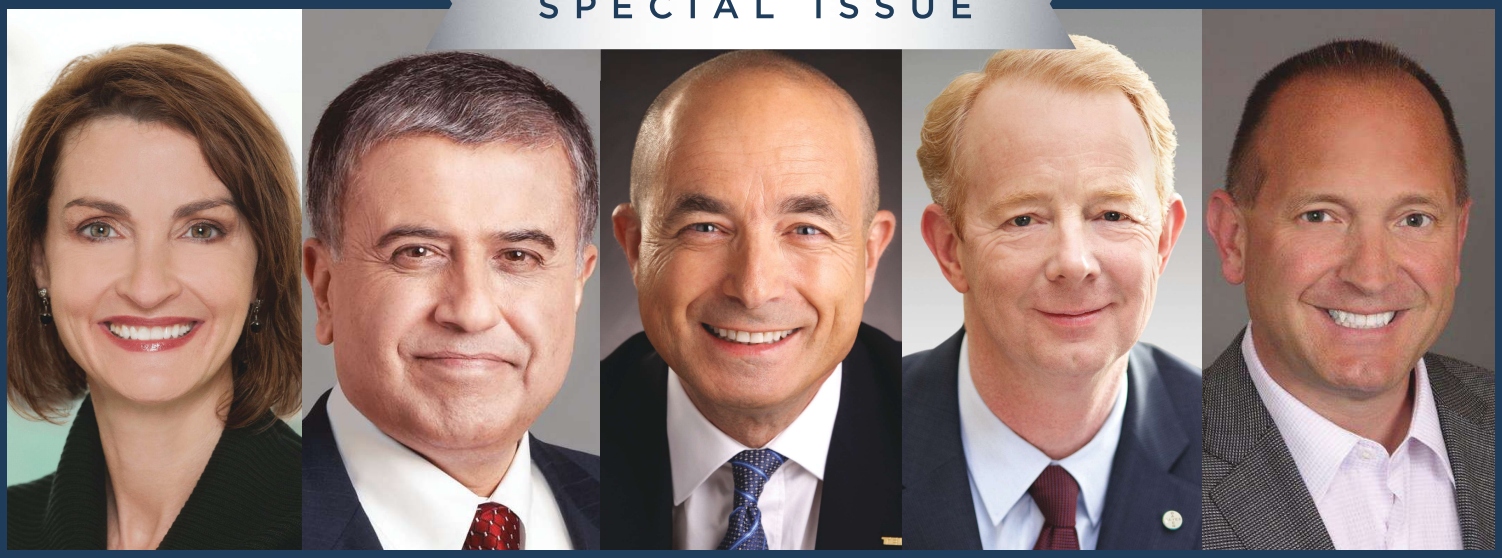

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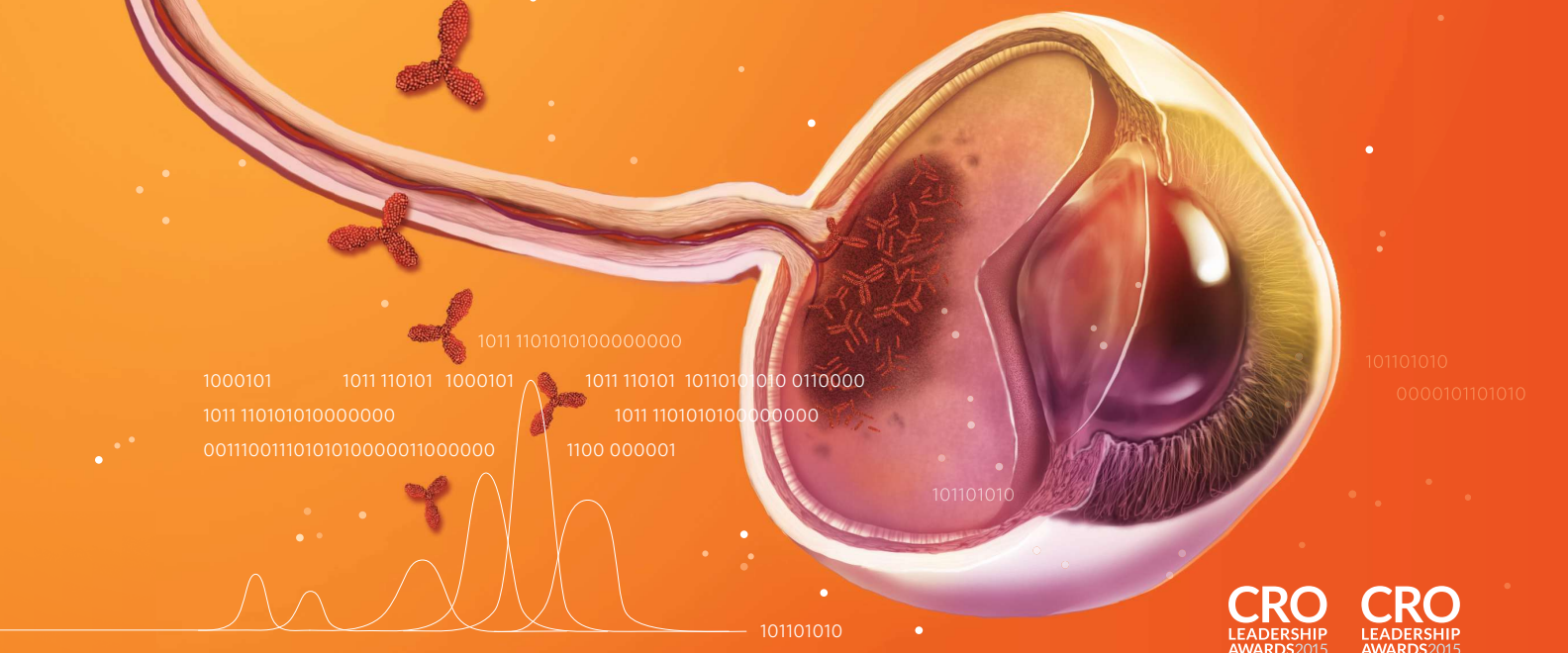

CRO LEADERSHIP AWARDS 2015 RELIABILITY

CRO LEADERSHIP AWARDS 2015 REGULATORY

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Key Trends For Biopharma In 2016 And Beyond

ROB WRIGHT Chief Editor

Dr. Ray Kurzweil, a futurist, inventor, pioneering computer scientist, and director of engineering at Google, believes that in the next 10 years 3D printers will be able to print human organs using modified stem cells derived from a patient's own DNA, thereby providing an inexhaustible supply of organs with no rejection issues. While Kurzweil's vision may seem based in fiction, there is already one company, Organova, designing and creating functional human tissues via 3D bioprinting technology. In biopharma, if we are to realize any semblance of the predictions of futurists like Kurzweil, our leaders must embrace an entrepreneurial and risk-taking spirit that transcends the mere ability to see and react to the latest trends.

Qu Biologics cofounder and CEO, Hal Gunn, M.D., put it succinctly when, during a recent discussion, he stated, "Opportunity in biopharma lies in doing things outside the way they are commonly done." Elizabeth Holmes is a good example of this philosophy. After dropping out of Stanford at the age of 19, she started Theranos with the goal of disrupting the $76 billion laboratory-diagnostic industry. Her idea was to eliminate blood vials and tourniquets and, instead, gather a very small amount of blood in containers (i.e., nanotainers) half the size of your thumbnail for diagnostic testing. Although the concept made Holmes America's youngest self-made female billionaire before the age of 30, it also has made her the target of the guardians of convention. Case in point, this past October the FDA declared Theranos' tiny vials to be "an uncleared medical device." Despite the FDA not having formal oversight for blood tests that clinical laboratories develop with their proprietary techniques, the agency opted to examine the nanotainers under its authority as a medical device regulator.

Prior to the FDA declaration, Holmes took fire from John Carreyrou, a journalist with the *Wall Street Journal*. In October, Theranos and its founder began bearing the brunt of Carreyrou's pen when he published a two-part series that called into question the company's business model. Not long after, in a *CNNMoney* article, Bill Maris, Google Ventures' managing partner, said regarding Theranos and Holmes, "In the life sciences space, you need MDs, you need PhDs." In other words, would nonscientist college dropouts like Elizabeth Holmes and Bill Gates please stop meddling in the life sciences? It's likely General Motors and Ford are thinking the same thing about Google with its self-driving car. But as Gunn insinuates, there are times when it is necessary to break from convention.

This month's signature issue represents an unprecedented move by the *Life Science Leader* editorial team. We reached out to the largest collection of biopharma trendsetters and industry insiders in our history to gain their outlooks for 2016. In the following pages you will find not only insights on industry trends across key disciplines but also the knowledge and wisdom to best prepare you for the coming year. We hope you like it and welcome your suggestions for how to make 2017's outlook issue even better.

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Q What's going to be big in biopharma in 2016?

A PRICING, PRICING, PRICING! A recent International Federation of Health Plans report shows that drug prices in the U.S. are up to 10 times higher than the same drugs purchased in other market economies. Our industry currently prices products to build in not only repayment for the product R&D itself in the shortest possible time but also to recompense for all R&D and failures. That model will not sustain itself much longer. Outrage at the 5,000-fold increase in price for an old generic toxoplasmosis drug by Turing flooded social media. There is a brewing backlash by politicians and payers alike to cap prices of important drugs that address medical needs of the country. We need to rethink our business model to address the now-serious challenges to off-the-charts pricing of biopharmaceuticals in the U.S., or others will rethink it for us.

CAROL NACY, PH.D.
is CEO of Sequella, Inc., a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed.

Q What global macro trends are going to have the biggest impact on biopharma in 2016?

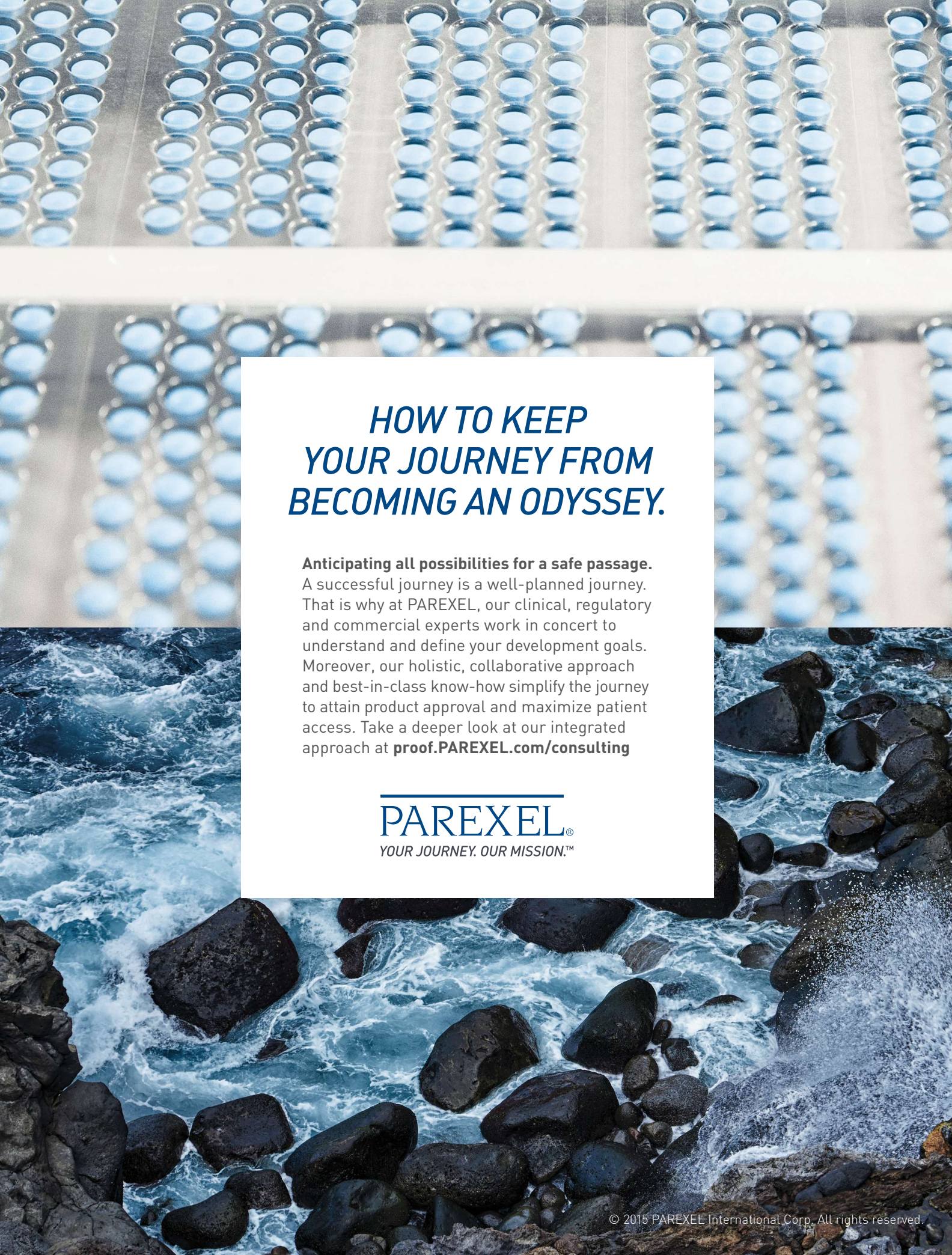
A BEYOND THE FOCUS ON THE SPECIFIC VALUE PROPOSITION of each new medicine and the actual and perceived pricing pressures on the biopharma industry (which will be at the forefront during the U.S. presidential campaign), the accelerating implementation of the Affordable Care Acts' policies and controls will alter the power structure and incentives throughout the healthcare system. Healthcare is moving to a centralized, policy-driven business, particularly as it relates to reimbursement. It will become increasingly difficult to differentiate new medicines and achieve returns necessary to incentivize the financial community to invest in risky and costly development programs which must be undertaken to address diseases that, if left untreated, have the potential to bankrupt the healthcare system.

KENNETH MOCH
is president of Euclidian Life Science Advisors. He was the former CEO of Chimerix, Alteon, and Biocyte and has 30 years of experience creating, managing, and financing biomedical companies.

Q What's going to be big in biopharma in 2016?

A PERSONALIZED APPROACHES TO TREATMENTS will continue to drive biopharma in 2016. The current belief is that personalized medicine allows us to better match patients to therapeutics based on their genetic profile. This needs to evolve, especially in the context of complex disease outside of cancer (e.g., autoimmune disease). Some have broadened the definition and taken a systems approach, using a large array of datasets mined by network analytics to identify targeted treatments. Many nonpharma companies such as GE and Dell have entered this space using cloud computing, pattern-matching, and Big-Data science. The fundamental issue with the current approaches is the belief that static data from patients coupled with state-of-the-art computing and analytics engines will generate predictive models to match a patient with a therapeutic. This assumes an individual's capacity to respond to a therapeutic stays constant over time, which we know is not the case. The key to unlocking the potential of precision medicine is the trifecta: therapeutics, diagnostics, and analytics.

LESLIE WILLIAMS
is president, CEO, and founder of ImmusanT, Inc., an early-stage company focused on peptide treatments for autoimmune diseases. She has more than 20 years of industry experience.



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Washington Outlook For 2016

JOHN McMANUS The McManus Group

A few weeks ago the GOP Leadership revealed that the House of Representatives will be in session for a mere 111 days in 2016, meaning it will be closed more weekdays than open. It will be in recess for seven consecutive weeks next summer. With so little time to legislate, virtually no must-pass legislation looming, and the focus turning to the 2016 elections, it is hard to see Congress enacting any significant health legislation next year.

However, it is not hard to envision that the focus on pharmaceutical pricing will intensify and, if not effectively countered, could cause a substantially negative perception to become engrained and lead to deleterious legislation in 2017, particularly if the Democrats win the White House and take control of the U.S. Senate.

This November, the Senate Aging Committee (an otherwise backwater, but for its subpoena power) announced a bipartisan investigation into pharmaceutical pricing. Ranking Member Claire McCaskill, Democrat from St. Louis, MO (the notable home of Express Scripts) said, "We need to get to the bottom of why we're seeing huge spikes in drug prices that seemingly have no relationship to research and development costs."

The Committee requested a massive number of documents related to marketing decisions and price spikes of specific products from Valeant Pharmaceuticals, Turing Pharmaceuticals, Retrophin Inc., and Rodelis Therapeutics. While the Aging Committee does not have jurisdiction to move legislation, it can certainly fan the flames on the matter.

In addition, all 18 Democratic Members of the House Committee on Oversight and Government Reform sent a detailed letter to Chairman Chaffetz (R-UT) requesting that he schedule a vote to subpoena Valeant and Turing CEOs regarding pricing of their drugs.

The immediate Congressional focus, for now, has been on a few companies. But there are now indications that the Obama Administration would like to broaden the debate to specialty drugs as well. The Department of Health and Human Services is convening a "public" (read: invite only) forum to examine the high costs of new drugs for grievous illnesses, noting, "Specialty medications represent only 1 percent of all prescriptions, but in 2014, these medications resulted in 31 percent of all drug spending."

While most Republicans are philosophically opposed to price controls, budget hawks are beginning to take notice of the allegations of increased drug spending. Earlier this year, Medicare's actuary disclosed that total spending on Medicare's Part D drug benefit will grow by 7.9 percent in 2015.

If the pharmaceutical industry is to head off deleterious legislation in 2017, it must effectively convey three key points in 2016:

1. **The reality of drug economics; the sky is not falling** — pharmaceuticals still comprise about 10 cents on the dollar as they have for years.

2. **Pharmaceuticals have made real-world patient-care transformations possible.** Hepatitis C can be now be cured in a matter of weeks with virtually no side effects. Since 1980, life expectancy for cancer patients has increased by about three years, and 83 percent of those gains are attributable to new treatments.

3. **The long-term value of innovation.** For example, a new treatment that delayed the onset of Alzheimer's by five years could save $100 billion annually in Medicare and Medicaid spending on Alzheimer's patients by 2030.

The real risk to the industry is a budget reconciliation bill in 2017, which seeks to curb federal spending and perhaps

reform the tax code. A newly elected president who campaigns on addressing "price gouging" of pharmaceuticals will try to team up with fiscal hawks in the Republican Party who may be more focused on trimming budget deficits than supporting pharmaceutical innovation.

The industry's challenge in 2016 is to change the current populist narrative on drug pricing and educate policymakers that preserving the U.S. free market is the world's best hope to curing grievous illnesses that still afflict millions.

IMPLEMENTATION OF PHYSICIAN PAYMENT REFORM AND ACA WILL IMPACT LIFE SCIENCES SECTOR

While Congress is unlikely to advance significant health legislation in 2016, there will be significant regulatory activity in implementing the recently enacted physician payment reform legislation that can have substantial ramifications on the life-science sector.

This spring, Congress enacted the Medicare Access and CHIP Reauthorization Act (MACRA), which repealed the dysfunctional Medicare physician payment formula which penalized physicians when their spending exceeded arbitrary targets and replaced it with a program that ties physician reimbursement, in part, to quality and resource use across all health sectors. Within a few years, nine percent of physician reimbursement will be based on physician practices' comparative success in delivering higher quality care and restraining total healthcare resources under the new Merit-Based Incentive Program (MIP).

The pharmaceutical and medical device industries are naturally anxious about a new payment scheme that utilizes metrics that could potentially penalize or reward physicians for prescribing their products. Physicians community, pharmaceutical manufacturers, patient groups, and other stakeholders will engage with CMS in a rulemaking process throughout the next several years to hash out quality and resource measures that will be used under the new payment system.

Initial measures are based on consensus group metrics endorsed by the National Quality Forum and the like, but stakeholders have the opportunity this year to point out gaps in measures and to develop additional measures that have the support of physician specialty societies and other expert groups. For example, the industry will want to ensure that prescribing certain expensive products or class of products, which are the standard of care, are accurately captured in quality metrics used to judge physician practices.

Even more transformative will be the new alternative payment models (APMs), where physician practices enter into capitated contracts with CMS for providing an entire episode of care. Most policy makers view this pay-for-value rather than "fee-for-service" approach as the future for Medicare. Think of the implications of a physician practice receiving a set payment for all cancer care delivered to a cohort of patients! Pharmaceutical manufacturers must engage creatively and demonstrate the value their therapies deliver.

Meanwhile, Obamacare staggers into its third year of implementation. Though it has been effective in reducing the number of uninsured, the increased coverage has been almost exclusively through expansion of the Medicaid program for the poor.

A recent report by Ed Haislmaier of the Heritage Foundation found that the number of Americans with health insurance increased by 9.25 million during 2014. However, the vast majority of the increase was the result of 9 million individuals being added to the Medicaid rolls. While enrollment in private individual-market plans increased by almost 4.8 million, most of that gain was offset by a reduction of 4.5 million in the number of people with employment-based group coverage. Thus, the net increase in private health insurance in 2014 was just 260,000 people. In all, Medicaid, not private health insurance coverage, accomplished 97 percent of the net increase in newly insured people, according to the study.

The Obama administration has dramatically lowered projections of the number of individuals enrolled in its exchanges. It is now predicting that 10 million will enroll in its exchanges in 2016 — 10 percent more than 2015. But that is 11 million, or over 50 percent lower than the Congressional Budget Office projected a few years ago. More than 80 percent of those enrolled qualify for income-tested subsidies.

This means the exchanges remain vulnerable to adverse selection whereby mostly sick and expensive individuals enroll and younger and healthier individuals remain outside the insurance pool. This can result in a death spiral of insurance premiums and, subsequently, enrollment.

Notwithstanding these troubling figures, the administration appears uninterested in making fundamental changes to the program. Therefore, bipartisan coalitions are focused on chipping away at the more offensive tax provisions of the sprawling law. Unions and businesses have formed an unusual partnership in repealing the so-called "Cadillac tax," which imposes a 40 percent tax on high-cost health plans. And the medical device industry has gained bipartisan traction in repealing the 2.3 percent excise tax on medical device sales. Repeal or modification of these two taxes is likely the only change to Obamacare that could get across the finish line in the next 12 months.

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.

Is Biopharma Consumerism The Center Of Commercial Innovation?

ALLAN L. SHAW

To say the recent public debate regarding biopharmaceutical drug prices has received a lot of attention would be a "British understatement." Interestingly enough, there have been no macro revelations from the intense media/political scrutiny of drug prices, which purportedly justified the biotech market sell-off. The industry's pricing headwinds are well-known, particularly in the face of global cost containment initiatives aimed at tethering unsustainable increases in healthcare spending. Thus, as Moody's Investors Services surmised, unsurprisingly, nothing tangible or sudden will come from all this political grandstanding apart from negative headlines for the forthcoming year, irrespective of regime change. Having said that, the horse is already out of the barn, and the shifting landscape is well underway. Consumer choice and cost-savings incentives established by direct (insurers) and indirect payers (pharmacy benefit managers or PBMs) are driving change in the industry's commercial model as the healthcare ecosystem continues evolving into a value-based system. Apart from being vastly different, how will biopharmaceutical sales and marketing look in 10 years?

The healthcare commercial environment is changing rapidly, shifting to more of a business-to-consumer model (as compared to B2B) in an effort to increase patient engagement. A good example of this emergent patient-consumerism is the proliferation of pharmacy "Minute Clinics" that offer patients (i.e., consumers) on-the-spot diagnosis and treatment along with instant prescription fulfillment — a system capitalizing on the fact that 80 percent of all consumer retail purchase decisions are made at the point of sale. Another trend is the switch to more OTC drugs (as compared to prescriptions) as part of product life-cycle management and the FDA's desire to enable patient-consumers to take responsibility for their own care, reflecting the general acceptance that certain conditions can be self-monitored and self-treated, such as erectile dysfunction, high cholesterol, or overactive bladders. As the patient-consumer becomes more educated and savvy, they will inevitably start to push back concerning the discrepancies in U.S.- versus international-branded drug pricing; drug prices in the U.S. are often two to five times those in Europe. Further heightening the stakes, the price controls in the rest of the world have put greater pressure on companies to capture ever-increasing profits in the U.S., underscoring the need to evolve, as the current model is clearly unsustainable.

It is important to recognize that purchasers, prescribers, and consumer-patients are considering price as a key component of a drug's expected health benefit. This trend reflects the increasing prevalence of patient-consumers bearing responsibility for an ever-larger portion of most healthcare costs driven by health insurance plans that have higher deductibles and higher copays. To better illustrate, if an oncology drug costs $120,000 annually, and one's co-pay is 25 percent, then the patient will owe $30,000 for a year's treatment, which is more than 50 percent of the median U.S. household income. This increased healthcare-cost burden is also the reason for the emergence of oncology drug TV commercials directed to patient-consumers; historically those commercials were viewed as a waste of money since physicians previously decided the choice of cancer drugs.

This dynamic empowers patients to make educated decisions about their healthcare purchases, much as they do when buying other consumer goods and services. In the new era of patient-consumerism, it will be all about product positioning, which highlights the strategic importance of optimal formulary inclusion for drug products (e.g., secured via drug manufacturer rebates), which is similar to retail shelf space for other consumer products (slotting fees paid retail product manufacturers), whereby commercial success can hinge on consumer or patient access. Without a formulary listing, over 95 percent of

drug-class purchases will go elsewhere (e.g., choose another drug product alternative).

As pricing headwinds continue, the disparity in gross-to-net pricing has never been greater (i.e., invoice brand price versus off-invoice price net of rebates, discounts and other adjustments/costs), reflecting in part the PBMs' emerging purchasing power (70 percent control of the commercial market given recent consolidation). While we are still quite far from a single payer system, the PBMs are currently defining the debate and are extorting ever-increasing rebates/discounts in exchange for favorable formulary positions (e.g., secure high-tier formulary status in exchange for a significant rebate and correspondingly lower patient-consumer co-pay). PBMs also have turned to formulary exclusions or restricted formularies as well as exclusive arrangements with drug manufacturers to fundamentally reduce market access for certain products to drive savings. For example, Solvaldi experienced a nearly 50 percent price erosion within one year of launch pursuant to AbbVie's exclusive distribution agreement through Express Scripts for Viekira Pak. This dynamic is further compounded by the increasing prevalence of high-deductible plans with higher out-of-pocket costs that are being partially mitigated by various forms of copay assistance, including coupons and vouchers. This domino effect is furthering the disparity in gross-to-net pricing that can exceed more than 60 percent in some instances.

Given the sheer magnitude of the financial stakes, it should not be surprising that a cottage industry has been created that has feasted on the inefficiencies and byzantine relationships embedded in the opaque biopharma supply chain. With so much value being lost or redirected, particularly in a pricing environment that is being challenged by the gravitational forces, isn't it time for the industry to start exploring ways to extend its commercial supply chain to better engage with patients and advance commercial goals while squeezing out the vast waste of legacy business practices? If not, these companies will be unable to claw back the margin that is being left on the table.

To start, biopharma must focus more on increasing brand loyalty by creating closer relationships with patients as well as other stakeholders who play a role in drug adherence and compliance. Patient noncompliance, particularly as rising out-of-pocket costs are hurting patient adherence, is directly related to the diminished value of pharmaceutical products. Establishing patient support programs is one solution. In my experience, drug adherence is the common denominator for all stakeholders and should serve as the foundation of any consumer strategy. Drug manufacturers, in tandem with stakeholders, need to implement discounting programs that correlate to disease management protocols that facilitate compliance, as opposed to simply trying to grow (or sustain) market share. For example, giving consumers price incentives on refills could become a loyalty strategy that uses discounts while generating other intangibles such as providing an opportunity for the industry to start rehabilitating its soiled image. Further potential benefits of reengineering the commercial model and extending the patient-consumer supply chain could include the following:

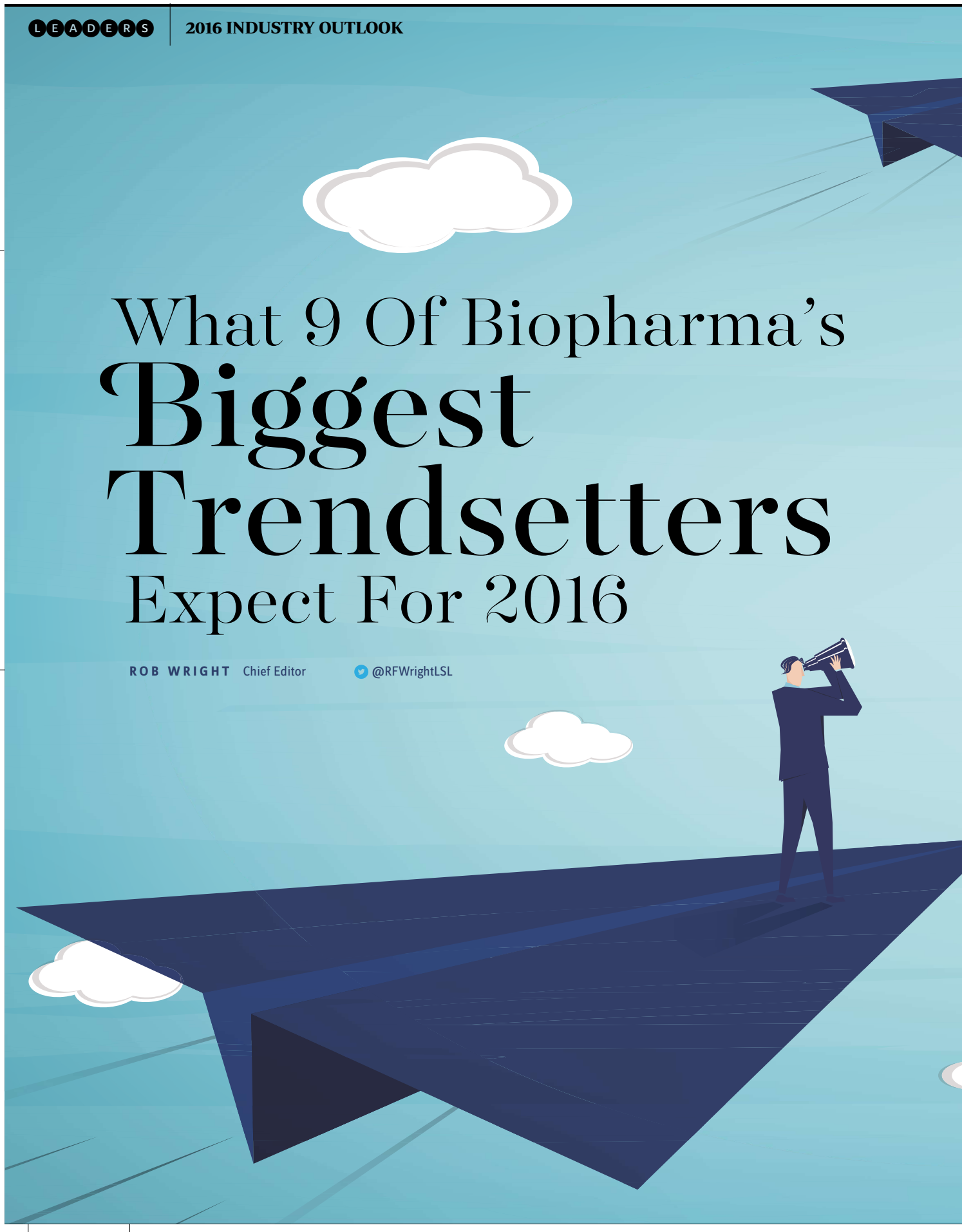
- Unimpeded access to the patient — understand the needs of our customers
- Undiluted brand positioning
- Offer a unique value proposition with superior products, tools, and services
- Capture incremental revenue within the patient-consumer value chain
- Increased contribution margin
- Secure loyalty to brands
- Drive market share
- Expand the market
- Influence trends and direction within target market
- Confirm leadership position via case management.

Healthcare consumerism is here to stay; the Internet and e-health have facilitated this, putting information and tools in the hands of the patient-consumer and not only for their benefit, but the entire healthcare industry's (e.g., gadgets, self-monitoring, and useful websites that help people track their conditions). Simple economics shows us that by empowering patients to understand and monitor their condition, thereby taking charge of their own lives and becoming an engaged patient-consumer, we can improve healthcare outcomes and reduce spiraling costs. Diabetes is an excellent example. By informing the patient-consumer about the benefits of managing their diet, regular exercise, and avoiding smoking, we can minimize the risk factors and positively affect outcomes. The step-change toward healthcare consumerism means that healthcare providers are increasingly targeting patients with their products. They are doing so in order to help/support patients on their journey to becoming more engaged and educated in their healthcare decision making. With this in mind, healthcare stakeholders must adjust to new ways of patient engagement to accommodate their needs in an evolving commercial model. If Fiat is already incorporating Viagra in its commercials, how long do you think it will before Viagra is marketed with Victoria Secret lingerie? We need to recognize that our business is changing from selling drugs (e.g., selling pills, injections) to delivering comprehensive solutions.

ALLAN L. SHAW is a senior biopharmaceutical executive/CFO. He is currently a member of the board of directors for Akari Therapeutics (chairman of the audit committee) and Vivus (chairman of the compensation committee). He was recently managing director – life science practice leader for Alvarez & Marsal's Healthcare Industry Group and was formerly the CFO of Serono. He has more than 20 years of corporate governance and executive/financial management experience and is responsible for more than $ 4 billion of public & private financings (including an IPO) and numerous business development transactions.

What 9 Of Biopharma's Biggest Trendsetters Expect For 2016

ROB WRIGHT Chief Editor @RFWrightLSL



Modern forecasters use a variety of means to deduce what may lie ahead. And while futurists utilize creativity, carefully structured surveys, computer simulations, and role-playing games in an effort to foretell the next big thing, one of their best predictive means remains the systematic scanning of news media and published scientific studies. The reason is simple. If you want to decipher the difference between an impossible-to-predict fad (e.g., the 2014 ALS Ice Bucket Challenge) and the underlying trend that drove the phenomenon (e.g., the ever-growing power of social media to influence and unify millions), it still pays to observe the actions of industry execs. Biopharma executives, responsible for allocating millions and billions of dollars that drive company strategy, are the life science trendsetters. To that end, *Life Science Leader* magazine asked nine executive-level decision makers to share their insider insights on what will be big for biopharma in 2016.

What Global Macro Trends Will Have Significant Bearing On Biopharma?

Dr. Marijn Dekkers

Chairman of Bayer AG's Group Board of Management

"We are in an unprecedented era where we are facing increased pressure to demonstrate the value of true innovation. Patients, doctors, regulatory agencies, and payers are scrutinizing much more carefully the value medicines offer. If a society wants to participate in and benefit from new therapeutic options and improved medical treatment, the economic success of R&D-intensive pharmaceutical companies is mandatory. That innovation will need to be rewarded to secure our business model — based on costly R&D. We as the biopharma industry have to clearly communicate, educate, and engage with stakeholders to demonstrate the difference between companies that bring novel drugs to market serving medical unmet needs and those companies that barely invest a dollar in innovation."

Paul Hastings

CEO and Chairman, OncoMed Pharmaceuticals

"Any time we have threats of a global slowdown or uncertainty surrounding interest rates, investors become risk averse. Likewise, uncertainties created by potential or actual changes in policies can deter investment. For example, if coverage, patent, or regulatory policies are uncertain or acting in opposition to innovation, investment is negatively impacted. Because small biotech is viewed as a high-risk sector, general investor aversion can translate to temporary pain for biotech entrepreneurs. What most people forget is that drug development can take a decade and overlap multiple economic cycles. To be able to ride out these three-to-five-year macro-economic cycles requires staged funding and good

policy. In 2016, we will continue to fight for a sound policy environment that supports investment in biomedical innovation [e.g., IP protection, small business tax and investment incentives, and the FDA's 21st century review]."

Rachel King
Cofounder and CEO, GlycoMimetics

"One of the biggest trends we will have to deal with in biopharma in the coming year is the need to address value and pricing in new ways. Until now, demand for our products has been fairly steady almost regardless of price. The industry will have less pricing flexibility than in the past, and each company will need to be even more focused on making the case for the value of its healthcare products. Since our industry drives innovation, I am confident we can make this case. Marginal improvements will not be rewarded in the same way as real innovation, and this should not surprise us. Tied to the need to deliver product value is ensuring that people have reasonable access to therapeutics that could help them. We will need to continue to fight for access while insurance companies increasingly limit policy coverage."

What Trends From Other Industries Will Leak Into Life Sciences?

Jeremy Levin
CEO and Chairman, Ovid Therapeutics

"The burgeoning of molecular diagnostic tools will continue to define drug clinical and developmental decisions. At the same time, digital technology will increasingly play a major part in ensuring patient adherence, managing prescriptions, designing and running clinical trials, and facilitating Big Data's use in drug discovery and development. Technological changes, along with the ongoing shifts toward personalized medicine in healthcare and patient-centered endpoints in drug development, are set against the backdrop of major business environment developments. For example, as payers and distributors continue to consolidate, they will demand an increased focus on outcomes and further pricing pressure, a process independent of government policymakers. Transformations in the generics industry, such as the emergence of biosimilars, will increase generic competition and industry consolidation while also reducing costs. Coupled with the erosion of the paragraph IV 180-day exclusivity provisions, three major players will be negatively impacted — Sandoz, Mylan, and Teva. These changes have the potential to push the generic industry to more aggressively use tools like the inter partes review (IPR) process to drive profits. In more forward-thinking companies, there is the possibility for the emergence of creative deals between the biopharma and generics."

Christi Shaw
U.S. Country Head, President Novartis Corp. and President Novartis Pharmacetuicals Corp.

"We already see how e-books and video-streaming services are giving consumers more choices for how they can almost instantly receive products or services. Healthcare will follow suit, with technology offering less invasive, more convenient and real-time diagnostic options, using smartphones and other portable and low-cost equipment. And, like ordering a book or movie online, you'll access these services from wherever you are, instead of making a trip to the doctor or hospital. According to market research firm IMS, the value of the U.S. telehealth market is expected to soar to $1.9 billion in 2018 from $240 million in 2013. As this market expands, so too will the range of options available to patients — from Waze-like apps that use crowdsourced analytics to anticipate health problems to devices that monitor the patient continuously and unobtrusively. Other intriguing ideas include technologies that can take blood samples during sleep and transmit the data wirelessly and automatically, and nanotechnology that can insert microscopic diagnostic tools into red blood cells to continuously monitor the patient."

> *"I'm confident we'll see expertise from tech and other successful consumer-focused sectors seeping into pharmaceuticals."*
>
> MARK TIMNEY

Mark Timney
CEO, Purdue Pharma

"While we've become much more patient-centric in recent years, biopharma still lags behind other industries when it comes to understanding and responding to consumers. In every sector of our economy, the consumer is more informed and empowered than ever. That's certainly true of the patients we serve, yet our industry is still figuring out how we can best engage and learn from them. I'm confident we'll see expertise from tech and other successful consumer-focused sectors seeping into pharmaceuticals, allowing us to further evolve and improve the services and support we provide patients."

Which Nontraditional Biopharma Companies Will Have The Biggest Impact On Life Sciences?

Dekkers

"Our ecosystem is evolving. For example, Big Data analytics are having a large impact on the way we practice life sciences. New players are bringing

What Is Required For Continued Healthcare Value Creation?

RON COHEN CEO Acorda Therapeutics, 2015 BIO Chairman

Just as we are on the verge of producing unprecedented medical innovation based on the acceleration of biological science, the politicized debate about pricing on medicine is set to derail this progress. This trend threatens to undermine our ability to produce new, more effective treatments for the diseases that afflict us, such as cancer and Alzheimer's. The discussions around these trends and biopharma's and other stakeholders' responses will have a major impact on biopharma in the coming year and beyond.

Start with the fact that biopharmaceuticals comprise just 10 percent of U.S. healthcare costs, yet relatively little focus has been on major drivers such as hospital costs (30 percent). In the U.S., we also have an outdated insurance model that focuses on cost rather than long-term value. Insurance companies' focus on cost alone limits access to meaningful treatments that could add years to patients' lives and cut down on overall healthcare, for example by reducing ER visits or hospital readmissions. In fact, according to University of Chicago economists, reducing cancer death rates by 10 percent would mean $4.4 trillion in economic value to current and future generations.

In the coming year, we will need to make progress engaging all stakeholders – life sciences companies, patient advocacy groups, healthcare professionals, public health experts, regulators and public and private payors – to develop innovative payment models that account for the societal and economic value of breakthrough medicines. Our goal should be to design an economically sustainable insurance system that ensures patient access and promotes a strong future for biopharma innovation.

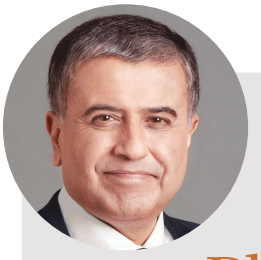
something different to the value proposition with greater focus on 'beyond the pill.' This leads to a need for companies to partner for mutual benefit to improve patient outcomes. Other applications of those technologies are also changing the farming practices in terms of decision making from farm data and insights. So, companies in the digitalization and data analytics space will become important partners for pharmaceutical and crop science companies in fulfilling each step of their core business: inventing, developing, and marketing new molecules which influence the biochemical processes in living organisms to make life better."

Hastings

"There are a lot of discussions going on about the potential of smartphones and wearables for collecting patient-centric data. The ability to obtain patient input in drug development and post-approval data collection is a top priority for the biopharmaceutical industry. The potential of technology is underscored by the recently published report by the Advisory Committee to the NIH director discussing recommendations for the president's Precision Medicine Initiative and Million Person Cohort. The report discusses the potential of these types of devices to further our understanding of patient needs and responses and how they could help us better understand how to diagnose, effectively treat, and prevent disease. As Google continues to restructure operations under the new parent company, Alphabet, we may see more innovation coming from this tech giant tied to the life sciences. For example, the Google contact lens is now being developed to allow people with diabetes to continually check their glucose levels via a nonintrusive method. Other firms may follow the 'IT-meets-medical-diagnostics' theme."

Levin

"As consumers become increasingly comfortable using sensory technologies, these products will progressively make their way into clinical trials and monitoring. As the role of mobile devices in capturing daily health data grows, it will not only be incorporated into patient care and clinical trials, but also we can anticipate electronic medical records being merged with new web-enabled tools that will promote better compliance with drugs and encourage consistent access to care. As healthcare providers continue to take a more active role in assuming



Fred Hassan: A Visionary Pharma Veteran

Fred Hassan, managing director at Warburg Pincus and former CEO and chairman of the board for Schering-Plough, believes companies like Apple and Google are trying to build "growth corridors" in healthcare. "Whether it will be applications related to the cloud, analytics, genomics, wearables, or a combination of all, healthcare is the new industry for IT," he says. In addition to the trend of nontraditional companies continuing to break into biopharma, Hassan sees another trend leaking in from other industries – leveraging culture and people management as a competitive advantage. "Google has done a great job enhancing its innovation productivity using this approach," he attests. "Big Pharma will start using more of this concept."

The three global macro trends he views as having the biggest potential impact on biopharma for 2016 are: (1) election year rhetoric in the U.S.; (2) continued economic recovery in Europe and Japan; and (3) important outcome readouts in Alzheimer's and cardiovascular research. Hassan explains his rationale for choosing these three trends:

Election Year Rhetoric

"The U.S. drives the appetite for R&D investment on a global basis. The price of Rx drugs will again become an election year catchphrase. This may affect investment in innovation, especially in the small pharma sector. This small sector gained good access to capital in recent years, but that may now start to change."

Continued Economic Recovery In EU and Japan

"After the U.S., the next two regions where there is some recoupment for investment in innovation are Western Europe and Japan. The economies of these two regions will continue benefitting from recent currency devaluations, and therefore, hopefully there will be an improved inclination to pay for innovation."

Important Outcome Readouts

"Hopefully, the large Alzheimer's trials such as Merck's BACE inhibitor study will read positive. There may also be positive news from one or more of the industry's ongoing cardiovascular outcomes trials. Only 5 percent of industry investments in R&D are in cardiovascular, yet this area remains the number one killer."

When Hassan was asked what he thought would be big for biopharma in 2016, he responded, "The biggest trend, which is already starting to happen, is the patient-centricity movement. Patients will continue to improve their health literacy (powered by the web). They also will pay more attention to their own care. Finally, they will become more active in making pricing purchasing decisions of healthcare (since more and more people will become exposed to higher deductibles, copays, and cost sharing)."

> *In 2016, we will continue to fight for a sound policy environment that supports investment in biomedical innovation.*
>
> **PAUL HASTINGS**

financial risks tied to patient care, there will be a growing role of linking the costs of care to outcomes. This will apply pressure to drug pricing. At the same time, digital marketing will soar, with those companies adept at providing platforms (e.g., Google, Facebook, Klick) increasingly edging out the more traditional marketing infrastructure."

What's Going To Be Big In Biopharma In 2016?

King

"I expect we will see actual new product opportunities come out of new technologies. Periodically, there are waves of excitement in our industry around new technologies or tools; an example was the early excitement over genomics, and now we see similar excitement about gene editing. New technologies hold promise to the extent they can deliver on specific new and needed treatments. When that happens, the focus sharpens on what actual therapies will be developed. Then real economics around both development and the ultimate market for such therapies come into play. I expect we will begin to see some specificity around product opportunities coming from some of the hot technologies. In some cases, that will mean increases in valuation (or validation of already high valuations). In others, companies may be challenged to justify valuations given actual opportunities they are identifying and pursuing. And all of this will be impacted — as we all will be — by the demand to demonstrate real value."

Shaw

"We'll continue to see new breakthroughs changing patients' lives. In particular, immunotherapy, which uses the human immune system to seek and destroy cancer cells, is one of the most exciting frontiers currently being explored in healthcare. The successful pairing of immunotherapies with targeted drugs resulting in a new combination therapy may offer more effective and lasting treatments. Current neuroscience research is also very promising, as new techniques, such as 'brains-in-a-dish' (i.e., human cells that have been transformed into brain cells) are allowing us to study the effects of new drugs in completely new ways. We are also exploring genome editing technology, which could potentially allow us to treat the genetic root of rare diseases by tweaking disease-causing mutations."

Timney

"Barring a major economic shock, I expect biopharma deal-making to continue at a rapid pace, buoyed by the recent correction in our sector. We may see large-scale M&A and divestitures, as well as more innovative deal structures as major players aim to share risk and refocus their product portfolios. As drug pricing remains in the spotlight, the emerging biosimilars market will be a hot topic of attention. And the global debate around international IP policies seems likely to reignite, especially as the Trans-Pacific Partnership takes center stage in U.S. electoral politics. On the innovation side, we're lucky to have a rich set of new scientific approaches entering the clinic. Among the areas that my team expects to receive heightened attention in 2016 are targeted therapeutics, gene editing technologies, nanomedicine, and microbiome therapies. We're also very interested in the movement toward patient-centric clinical trials as a means of both improving trial recruitment and learning how to better serve patient needs."

CURES: A Big Theme For 2016

Patrick Vallance, president of pharmaceuticals R&D at GSK, believes cures will be a big theme in 2016. Here's why. "A better understanding of genes, targets, and human disease is allowing us to move beyond symptomatic treatments and instead focus on truly modifying the pathway of disease – halting or reversing progression," he states. "This is already true for some infections [e.g., advances in Hepatitis C]." According to Vallance, approaches to curative or long-term remission for Hepatitis B and HIV/AIDS are areas attracting a lot of attention. "Modulation of the immune system is clearly going to have a further big impact on the management of auto-immune and inflammatory disorders," he attests. "In 2016, we will begin to see combination immuno-oncology approaches in the clinic."

Vallance believes informatics and data sciences are the keys to improving drug discovery and delivery of healthcare. "Commercial organizations have been using data and advanced analytics for years to better understand their customers," he says. "To accelerate and improve the efficiency of drug discovery, research organizations must access similar tools to mine and link the data being generated from things like the human genome, electronic health records, wearable sensors, and mobile devices." Having access to this kind of data creates a paradigm shift in our industry. For example, it changes the way we select targets for drug discovery, determine whom to enroll in studies, and establish the responder population in the real world. Vallance says that with informatics and data sciences "We are going beyond small molecule chemistry and antibody therapies as the only options for change. In 2016, we will firmly be in the era of therapies based on oligonucleotides, cell, and gene therapies."

5 Manufacturing Trends Aimed To Support The Biologics Boom

TRISHA GLADD
Executive Editor
@TrishaGladd

In today's pharmaceutical market, biologics make up nearly 20 percent of total sales. However, by 2020, it is expected they will account for slightly more than half of the world's top 100 selling drugs. As we move into 2016, the biomanufacturing industry will look to new technologies, processes, and relationships to support this dramatic shift in patient care. To find out what effect this will have on biopharma in the year ahead, I gathered insights from some industry experts. Below are the top five trends they think will have the greatest impact.

1 Continued Development Of Flexible Manufacturing Solutions

The biologics boom that is anticipated to take place in the next five years is a result of several manufacturing-focused trends, including the increase of product titers and yield, the adoption of single-use technology (SUT), and localization of manufacturing. Combined, these trends have created a greater interest in flexible manufacturing solutions, which, according to Parimal Desai, VP of global vaccines and biologics commercialization at Merck, is a trend we can expect to continue. "2016 will bring more focus on developing flexible manufacturing solutions to meet a wide range [high-volume to niche products] of capacity needs, as well as to address increased demands for localization of manufacturing into emerging markets. This shift will require companies to implement more continuous manufacturing and invest in single-use technologies and flexible manufacturing plants with rapid changeover procedures as well as the use of in-line process analytical technologies," he explains.

SUT, an integral part of the flexible facility concept, also faces barriers to adoption, specifically when it comes to the standardization of both equipment and extractables and leachables testing. While Chuck Hart, director of manufacturing at Prolong Pharmaceuticals, says he expects single use to continue to grab headlines, he recognizes that understanding this and other issues is an area where focus needs to continue. Stronger partnerships between

SUT vendors and biopharma manufacturers is absolutely critical, not just for the advancement of single use but also for the future of biopharma. This past year, we saw some advancement in this relationship through a project coordinated by David Wolton, a biotechnology consultant with PM Group, an international engineering design, architecture, project, and construction management firm. Wolton worked with some industry vendors to come up with the concept of offering a "store" of standardized single-use parts on supplier websites. The ultimate goal is to offer interchangeable single-use parts, so there are more choices for the buyer and increased opportunities for suppliers. Solutions provider JM BioConnect launched the first site offering standardized single-use equipment last month. Other suppliers are expected to follow in 2016.

When it comes to the standardization of extractable and leachable testing, the Extractables Work Group of the BioPhorum Operations Group (BPOG) made progress with the release of the Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing in November 2014. BPOG member companies are now adopting the protocol as their user requirement and are in the process of communicating this to their suppliers. BPOG will support implementation of the protocol by helping to build understanding and consistent application across suppliers. Numerous suppliers are already moving toward adoption. Compliance is expected by the first quarter of 2017. And while the focus is on implementation, BPOG's efforts to create an American Society for Testing and Materials (ASTM) extractables standard that meets the needs of biologic drug manufacturers will continue. The team is also developing a leachables testing best practice guide to compliment the extractables protocol.

Overcoming the challenges of SUT wouldn't just accelerate its adoption; it would also establish the technology as a qualified tool in the application of continuous manufacturing, an approach that offers efficiency and agility to drug production. While some companies, such as Bayer, Genzyme, and Novartis, have manufactured a small number of products using elements of continuous manufacturing, there is still more work to be done when it comes to creating a successful end-to-end continuous process. At the 2015 BioProcess International Conference and Exhibition, Konstantin Konstantinov, VP of technology development at Genzyme, delivered a presentation on the future of continuous processing in biomanufacturing. "We'd like to see the dominant design [for continuous manufacturing] as starting from the media throughout the entire process to drug substance and perhaps even beyond to incorporate the drug product in a continuous line. However, this is not going to be enough. In order for a process like this to exist and function properly, it's very important that it's equipped with an integrated control system, which is often underestimated."

Finally, we may see an increased use of prefabricated facilities, such as the KUBio biopharmaceutical factories recently introduced by GE Life Sciences. The first KUBio factory was shipped in September from Germany to China. It was bundled in 62 containers and assembled and built in 11 days. There are several benefits to these facilities, including shortened time to market and a significant reduction in costs (e.g., GE claims KUBio can reduce costs by as much as 45 percent).

2 Closer Partnerships Between Industry And Regulators

According to Desai, this trend will be key to the rapid progression of the industry and the introduction of innovative concepts in biopharmaceuticals. "With initiatives like the breakthrough therapy designation, regulatory agencies, such as the FDA, have engaged in close dialog with industry. This has truly enabled getting life-saving medicines to patients quicker while not compromising quality," he explains. "It would be very good to see other regulatory agencies around the world also be more receptive to such discussions early in the product-development life cycle."

Hart thinks 2016 will be a year that moves us much closer to regulatory standards across the globe. "The regulatory harmonization I'm seeing is very exciting," he says.

> *Having a single standard would simplify things significantly and would make the market even stronger.*
>
> CHUCK HART

"As companies prepare for pre-approval inspection, they prepare based on the regulatory agency. For example, in the past, the EU was more interested in area cleanliness and autoclave data while the FDA concentrated on processing. Having a single standard would simplify things significantly and would make the market even stronger." Hart says he believes the continued efforts of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) will have an even greater impact on the industry. As companies recognize regulatory efforts toward global standardization and that the FDA is truly working toward up-front partnerships, Hart expects the ability to develop world-class quality organizations within companies will become easier.

He adds that he also sees a trend with the FDA acting more as a partner than a big brother. "Instead of being perceived as a bully, the FDA seems to now be working toward up-front meetings and collaborative discussions about the path forward. In my opinion, the auditors are being trained better to really work with a company, and unless its GMP violations are egregious, the FDA works more as a partner to resolve any gaps."

Will Today's Biopharma Trends Impact The Rising Immunotherapy Market?

> *Moving forward, we are likely to see new, perhaps disruptive, technologies for gene transfer.*
>
> MARC BETTER

According to a recent market research report, nearly 50 percent of today's oncology drug market is made up of cancer immunotherapy drugs. More importantly, though, is the fact that this market is expected to nearly double in value ($41 billion to $80 billion) in the next five years. Marc Better, VP of product sciences at Kite Pharma, a biopharma company focused on developing immunotherapy products, discussed with me some of the opportunities and challenges in this electrifying market.

Q: What biopharmaceutical trends are you most excited about?

A: We are seeing a trend now toward automated solutions for the handling of liquids that can, at least in theory, be integrated into commercial manufacturing operations. Concurrently, we are seeing new solutions for managing the entire process flow, thereby allowing real-time management of the manufacturing process. In addition to new equipment that is being developed for industrial use, systems for real-time tracking of the product during the manufacturing process are being developed by a variety of suppliers.

Q: Are there any trends you think will be problematic for the growth of the cell therapy market in 2016?

A: As the excitement in this area has grown, we have seen a tremendous increase in the number of new entities (academic, biotech, and pharma) working in this space. This has resulted in increased demand on CMOs that support this industry. CMOs of cell therapy products, as well as other contract vendors that support this industry, may be stretched to meet this growing demand, which could eventually outstrip the current available capacity.

Q: How are you preparing to face these trends?

A: We see investment in process automation as a valuable option to bring important new products to patients who need them in a cost-effective and efficient manner. To help bring our products through clinical development, we are also investing in both clinical and commercial manufacturing organizations. Kite has built a clinical manufacturing facility near its headquarters in Santa Monica, CA. Once this facility is fully qualified, we will have capacity to produce more than 300 autologous T-cell products per year for clinical trials. In addition, Kite is building a commercial manufacturing facility in El Segundo, CA, for KTE-C19, our anti-CD19 CAR T-cell product for lymphoma and leukemia. We expect to complete construction by early next year and be ready to support commercial launch of KTE-C19 by 2017.

Q: What advancements in cell therapy need to happen in order to see continued growth?

A: In the immunotherapy space, we are looking forward to new technologies to bring new genes into cells as well as target-specific cellular proteins to either increase cell therapy effectiveness or overcome inhibitory signals. Currently, there is a variety of means to introduce new genes into cells using either viral vectors or nonviral mediated gene transfer. Moving forward, we are likely to see new, perhaps disruptive, technologies for gene transfer. We are also likely to see considerable advances in technologies for gene editing that may allow gene therapy products to provide enhanced functions in vivo. Together, these technologies should allow rapid production of cell therapy products that are both more effective and more specific than what is possible with the technology available today.

3 The Need To Foster New And Existing Talent

According to a December 2014 McKinsey & Company report, "Biopharmaceutical companies best positioned to succeed in tomorrow's market will be those that master a broad set of technical and operational capabilities." To accomplish this, Desai says there needs to be a sustained effort and commitment to develop and permanently embed these capabilities into an organization. For example, at Merck he says they are focusing on the development and retention of technical and scientific talent.

To master technical and operational capabilities, Merck is also focusing on developing simple and innovative business systems to enable rapid and successful decision making. "Success in this area will result in more effective management of complex technical programs and a shortened CMC [chemistry manufacturing and controls] development cycle while also ensuring that CMC deliverables are right the first time," he continues. "It will also enable managing more programs in parallel without substantial increases in the workforce." Finally, he believes the rapid growth in biopharma seen over the past several years will result in increased competition for a finite pool of experienced and skilled talent who are able to create and execute the strategies and tactics needed to succeed in the marketplace.

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Desai says companies also should be aware of the state of new talent being recruited into industrial jobs, particularly when it comes to their training and development. "We are finding that fresh graduates do not have a good understanding of the drug development process and need a significant amount of on-the-job training." He adds, "Academic programs should seriously consider how their curricula could cater more toward actual industrial applications." In a recent article on OutsourcedPharma.com, Kamal Rashid, director of the Biomanufacturing Education & Training Center (BETC) and research professor at Worcester Polytechnic Institute (WPI), says an adequate source of workers is possible in the U.S. biomanufacturing industry if they can acquire additional training in specific skillsets. "For example the industry wants people who know the chemistry of a protein and how to purify it and what's involved in the post-translational modifications in the mammalian cell that's not available in microbial cells," he says. Of course, this additional training can be both costly and time-consuming. A recent report by Eric Langer, president and managing partner of BioPlan Associates, states that this cycle can be broken by stronger relationships between employers and universities.

4 Industry Collaborations

As more companies enter the biologics market, the need to seek out talent and expertise not just in recent graduates but also in partners is expected to increase. According to Nice Insight's report on 2015 outsourcing trends, 62 percent of those surveyed spent $10 million to $50 million USD (2014-2015) on outsourcing, which is a 24 percent increase over the year before. In an article published in *Life Science Leader*, Nigel Walker, managing director of That's Nice, states, "The demands from industry service providers have never been greater. Some key trends driving the continuously rising outsourcing budgets include a growing pipeline of biologics, complex therapies and delivery systems, and precision-based medicines, as well as larger, more complex clinical trials,

> *2016 will bring more focus on developing flexible manufacturing solutions.*
>
> PARIMAL DESAI

real-world evidence studies, and the need for sophisticated new technologies, all of which require advanced, integrated expertise." He adds that this trend of turning to partners for a variety of aspects of drug development is "partly to avoid the very high capital expenditure and long lead times needed to construct, equip, and validate manufacturing facilities. Outsourcing is an efficient, cost-effective way to meet these rapidly changing industry needs." Scott Lorimer, global VP of biologics at Patheon, says partnerships are exciting for the entire biopharmaceutical sector, not just CMOs. "These partnerships are mutually beneficial and result in drugs getting fast-tracked to the clinic, reaching the market in optimal time. By partnering with biopharmaceutical services organizations, the biopharmaceutical industry is effecting accelerated development and launch of exciting new originator medicines, biosimilars, and biobetters alike."

Desai believes partnerships between traditional pharmaceutical companies and small biotechs may also grow in 2016. "Competition for access to innovative technologies and the next generation of therapies will result in higher valuations for new and, as yet, unproven technologies. This, in turn, will result in higher prices being paid by the traditional pharmaceutical companies for rights to these assets." This is especially true in the area of immunotherapy, where pharma companies are all fighting for the piece of a pie that experts anticipate to be worth $80 million by 2020. A leader in the immunotherapy space, Novartis, made headlines earlier this year when it partnered with Aduro Biotech, committing to pay $200 million up front for Aduro's Sting technology and another $500 million later in milestone payments. In June, a landmark deal was made between Celgene and Juno, with Celgene paying $1 billion for Juno's pipeline of CAR-T drugs.

5 Presidential Election Will Increase Spotlight On Drug Pricing

The cost of pharmaceuticals is becoming more and more prevalent in today's news coverage, and according to Hart, there should be no expectations for it to go away any time soon. "Unfortunately, with 2016 being an election year, we will continue to see a heavy push toward reduced drug costs," he says. "Candidates will have a field day with headlines like the 5,000 percent mark-up of Daraprim. This is concerning because, based on my experience, I have a very good sense of both the up-front and sustainable costs to produce biologics, and it just cannot be done inexpensively without sacrificing quality." Desai agrees that sticker shock as well as the cost of new breakthrough and lifesaving therapies (e.g. $1,000/pill announcement for Harvoni) will continue to fuel these conversations. "Pressure will increase to contain drug costs, and rhetoric on biopharmaceutical pricing will increase in the run-up to the upcoming U.S. presidential election."

It is no secret that some drugs do come with a high price tag. However, when you look at the recent report from the Tufts Center for the Study of Drug Development citing the current cost of bringing a drug to market at $2.6 billion, the solution becomes clearer: Lower the cost of making the drug, and you can lower the final price tag. So while the presidential candidates continue to battle into the primaries, pharma can only continue to look at ways to reduce R&D costs, just as Desai says Merck will be doing in the next year.

Dr. Gargi Maheshwari and Dr. Graham Tulloch contributed to Dr. Desai's input for this article.

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What 2016 Will Bring For Biosimilars

ANNA ROSE WELCH Executive Editor @AnnaRoseWelch

One of the biggest trends of 2016 is surely going to be the emergence of the biosimilar market in the U.S. following the launch of the first product (Zarxio) in recent months. Biosimilars have been available in the EU for roughly 10 years, but in the U.S. there are still a number of key decisions that need to be made regarding a biosimilar's name, label, and interchangeability. As such, the U.S. regulatory pathway is still taking shape. We spoke with some industry experts to get their predictions as to what the most important biopharmaceutical industry trends will be in 2016 and how those trends will affect the biosimilar market.

What biopharmaceutical trends are you most excited about, and why? How do you expect these trends will impact the biosimilar market into 2016?

Alan Sheppard ▸
Principal, Global Generics, Thought Leadership, IMS Health

"Significant clinical advances are now being made in biopharmaceutical therapies which are meeting previously unmet clinical needs. The costs of these therapies, though, are putting unprecedented strain on drug budgets and an increasing demand for patient access. As biologics prices continue to rise in 2016, the industry is going to be paying closer attention to biosimilars and their cost advantages."

Craig Wheeler ▸
President and CEO, Momenta Pharmaceuticals

"You're going to start seeing more complex products come into the market with the biologic-manufactured products, and I think that will begin to tailor how the biosimilar market is actually going to evolve in the U.S. It will be very interesting to see some of the first antibodies that get to market. I think those are the more complex molecules. You saw Sandoz's approval, which was a protein, but not a glycosylate antibody. When you start to get into the more complex molecules, we need to watch if the FDA continues its trend of approving biosimilars with full extrapolation and full brand labels, or if it's going to start to limit the labels to what trials were done."

Bert Liang ▸
CEO and Executive Director, Pfenex and Board Chair, Biosimilars Council

"We are living in an exciting time for the biopharmaceutical industry. Innovative therapies that doctors — including myself — could once only dream of are now available to treat patients with chronic diseases. However, the costs of some of these treatments are exorbitant. In response to this, increasing the availability of cost-effective biosimilars will play a huge role, allowing more patients to reap the benefits of the life-changing drugs made possible through medical advancements, without crippling healthcare systems."

Mark McCamish ▸
Global Head, Biopharmaceutical Development, Sandoz

"I would highlight the progress on immuno-oncology. This area is an outstanding example of how biopharmaceutical trends appropriately follow the science and create truly breakthrough therapies — in this case by harnessing and stimulating our own immune systems to fight diseases such as cancer. The approval of checkpoint inhibitors marks only the beginning of this new era in medicines. This ongoing innovation continues to create wonderful opportunities for patients but also great opportunities for biosimilars now and in the future. That is, biosimilars currently being developed can help offset costs of older biologics that are off patent, allowing health systems to create headroom in their budgets to fund these newer innovations. As we have seen in Europe and other countries, biosimilars create competition, which leads to savings for healthcare systems and increased access for patients."

Biosimilar Trends That Could Be Problematic In 2016

It's no secret that, when it comes to the U.S. biosimilar market, there are still many important decisions that need to be made by the FDA. The agency's rulings on naming, interchangeability, and labeling will no doubt determine the uptake of biosimilars and the initial success of the market in the U.S. But among biosimilar experts, there are also concerns related to patents and data exclusivity for reference products that could also be problematic for the growth of the global biosimilar market. Pfenex's Liang says there are still a number of questions pertaining to the resolution of the Trans-Pacific Partnership (TPP) negotiations. "Globally, more clarity is required in the interpretation of the TPP's exclusivity period for biologics — whether this is a period of market exclusivity or data exclusivity — to understand potential ramifications on biosimilar market growth in the future."

In addition to concerns about data exclusivity of biologics, those paying attention to the rise of the biosimilar market should look at what is happening in courtrooms with the patent dance and biologics patent challenges. Both Liang and Wheeler address the 351(k) pathway and the impact its formation will have on the rise of the biosimilar market. As Liang states, "Similar to the Hatch-Waxman legislation which created the generics industry, decisions by the courts also will play a large and impactful role in clarifying the 351(k) pathway, with significant ramifications in 2016 — and obviously beyond — for the pathway for biosimilar development in the U.S."

In fact, Wheeler singles out the 351(k) pathway as being one of the biggest complications for the biosimilar legal clearance process. He homes in on the Federal Circuit's final decision regarding the Amgen v. Sandoz "patent dance." "This whole patent exchange, which is already being litigated, makes it much more complicated than the generics side of the world where there's the *Orange Book*, and you know what patents you're dealing with before you even start developing a program," says Wheeler. There is also the matter of the inter partes review (IPR) process, which promises a more timely and cheaper method of challenging patents. In fact, it is currently being employed by biosimilar makers such as Momenta. However, branded pharmaceutical makers are arguing in favor of patent reform legislation that would bar generics and biosimilar makers from using the process to get their products to market more quickly. As Wheeler says, questions remain, such as, "How long will the IPR process take, and will the IPR process continue to be accessible to biosimilar makers with some of the patent reforms that are actually out there?"

> *We're working very aggressively on preparing for the next round of the Biosimilar User Fee Act.*
>
> CRAIG WHEELER

Education: The Biggest Goal Of 2016 Biosimilar Industry

Drug companies, regulators, doctors, patients, and payers all hold the keys to the success of the 2016 biosimilar market. In order to build a sustainable biosimilar market, more education will be needed to address doctor and patient hesitation to ensure these medicines are prescribed. Companies will need to remain stalwart in navigating the evolving U.S. regulatory pathway amidst ongoing lobbying efforts and emerging global regulations. Here, *Life Science Leader*'s panel of biosimilar experts share how the industry and their companies plan to address the challenges currently facing biosimilars moving into 2016.

How are you/your organization preparing to face these trends in 2016?

"We must continue educating policymakers about the potentially far-reaching implications of biosimilar regulations in the U.S., as well as the globally impactful Trans-Pacific Partnership (TPP) deal. We are confident that leaders

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in both the U.S. and globally will enact policies to support the development of biosimilars. As board chair of the Biosimilars Council, I spend a considerable amount of time within these educational efforts. In particular, within the Biosimilars Council and at Pfenex, we are focused on explaining to legislators the science behind biosimilars, including the safety and efficacy of these therapeutics, particularly given the decade of experience in other geographies such as the EU and Australia. Through ongoing meetings with policy and decision makers, we continue to inform on the important role of biosimilars in the future of the U.S. healthcare system and the value that increased patient access and competition can bring. We are committed to advancing this dialogue and offering research and insights to all stakeholders, from patients to physicians to lawmakers and regulators."

Bert Liang

"We continue to advance our pipeline of biosimilars and expect to make several new biosimilar regulatory submissions in 2016. We will focus on increasing uptake of our first biosimilar in the U.S. and preparing for launches of our next generation biosimilars, both in the U.S. and EU. Globally, we will also continue our outreach and advocacy efforts to improve stakeholder understanding and acceptance of the biosimilar concept, as this is key for the continued growth of this industry."

Mark McCamish

"We're working very aggressively on preparing for the next round of the Biosimilar User Fee Act (BsUFA) negotiations. We're doing so to make sure the pathway allows us to actually use the technology and science we have and to try to abbreviate the trials necessary to get extrapolation and interchangeability more quickly. Our company's approach to biosimilars is built on designing products that have fingerprint-like similarity. We are trying to engineer biosimilars that are very, very close to the brand and remove any residual uncertainties through our characterization and understanding of the products and our engineering them. It's very important to us that the FDA pathway allows us to take advantage of the technology investments we're making and to be able to gain efficiencies in the approval process."

Craig Wheeler

"Lobbying by originator companies is being used as an effective tool to create doubt within the biosimilar market. Biosimilar companies will need to address policymakers to reinforce the positioning of biosimilar medicines within a clinician's armamentarium as a tool to increase patient access and provide the ability to treat more patients for less cost."

Alan Sheppard

The Countries/ Companies That Will Make The Biggest Impact On The Global Biosimilar Market In 2016

To date, a majority of companies exploring biosimilar development has chosen to direct their energies toward the more established EU market. However, despite the current strength of the EU market, it was surprising to discover that most of the experts we interviewed did not choose the EU market as the one to watch for 2016. So where are they directing their attention?

According to Tim deGavre, the chair of the biosimilar sector group of the British Generic Manufacturers Association, the U.S. is poised to make the biggest difference in the space because of its scale and because it is tackling important decisions related to interchangeability and naming. He calls

attention to the recent approval and release of Sandoz's Zarxio, along with the FDA's ongoing review of several other biosimilar applications, including etanercept and infliximab, as being important steps for the growth of the global biosimilar market.

Liang also singles out the U.S. because of the FDA's recent efforts to clarify the biosimilar regulatory pathway. According to him, "A recent report found the FDA has spent more hours reviewing biosimilar applications in 2015 than in the three previous years combined. This momentum is anticipated to continue, and 2016 is when we expect to really see the industry blossom." In addition to the FDA's efforts, McCamish draws attention to payers, stating "We expect payers to increase their efforts to support the uptake of biosimilars, both in the U.S. as well as in the EU."

But beyond the efforts of the FDA and the size of the country, Wheeler is focusing on some of the players within the U.S. In particular, he identifies the recent Pfizer and Hospira merger which led to the creation of a large and highly reputed biosimilar portfolio. According to Wheeler, the Pfizer and Hospira deal "is quite a potent combination in the marketplace. The resulting company could actually make some real waves with the combination of portfolios it's going to have with that merger."

The 2016 Biosimilar Market: A View From The U.K.

While the U.S. market introduced its first biosimilar medicine only several months ago, biosimilars have been available in the U.K. since 2006. Recently, England's National Health Service (NHS) took proactive steps toward promoting biosimilar education in order to bolster market growth and consumer/doctor faith in these cost-saving biologics. When it comes to looking ahead into 2016, Tim deGavre, chair of the biosimilar sector group of the British Generic Manufacturers Association (BGMA), says the industry, and especially the U.K., should expect to see continued growth in the biosimilar market.

As patents expire for reference molecules, biosimilar makers will be ramping up their development to bolster the biosimilar pipeline, ushering in a large number of cost-effective drugs for patients suffering from rheumatoid arthritis, cancer, and diabetes. In the face of a growing number of highly priced biologic drugs targeting the aforementioned indications, deGavre says the U.K. should expect to see the biosimilar market lead to hundreds of millions of pounds of potential savings for the NHS. In particular, deGavre references a study that examined the cost burden of using human growth hormone (hGH) and the impact the uptake of hGH biosimilars could have on annual healthcare. "Data based on 2010 usage of hGH at The North Central London Formulary and Medicines Management Group at University College London Hospitals NHS Trust suggests annual cost savings in excess of £200,000 [$300,000] per annum are possible from a single center if all patients were switched from originator hGH to biosimilar hGH," says deGavre.

However, there are a number of roadblocks that could prevent the U.K. biosimilar market from achieving growth in 2016. For one, deGavre says there are issues with the decision-making process within the U.K. which stand to impact biosimilar prescribing habits. For instance, deGavre says there are an increasing number of decision points on the path to prescribing a medication, as the NHS has left the decision-making process to locally accountable organizations. "We are seeing a lack of clarity and high levels of variation as to who is responsible for making the decisions in each locality, resulting in some inertia in decision making in new and complex areas of medicine," deGavre states. "This is creating significant variability in decision making in the take-up of all medicines but especially in new medicines such as biosimilars." deGavre calls attention to Norway and Denmark as examples of how a national approach can lead to significant uptake of biosimilars. Norway in particular has turned heads with its 69 percent discount – a discount so steep, it has made it difficult for prescribers to resist the biosimilar. According to an article published by Bloomberg in April 2015, this discount on Orion Oyj's biosimilar of Remicade led doctors to increasingly prescribe the biosimilar, which quickly captured 50 percent of the Remicade market.

Much like in the U.S., deGavre also points to the number of concerns that persist about the quality, safety, and efficacy of biosimilars in the U.K. There is still a general need for acceptance of the science of biosimilars, the Medicines and Healthcare products Regulatory Agency (MHRA) pathway, and extrapolation. "In extrapolation, a biosimilar only needs to prove it is safe and effective in the most 'sensitive indication,'" explains deGavre. "Where the mode of action is the same, clinical studies for each of the additional indications are not required. Communicating this important principle of biosimilarity will be critical to the acceptance and use of biosimilars in the U.K."

The NHS has taken a key step toward improving biosimilars communication and education to decision makers in the U.K. In recent months, the NHS collaborated with several organizations, including the Association of the British Pharmaceutical Industry (ABPI), The National Institute For Health and Care Excellence (NICE), and the BGMA, to release a document entitled *What Is A Biosimilar Medicine?* The purpose of this document, as described in its introduction, is to "provide an update for key clinical and nonclinical stakeholders about the developing role of biosimilar medicines in the NHS in England and to support the safe, effective, and consistent use of all biological medicines, including biosimilar medicines, to the benefit of patients."

> *We are seeing a lack of clarity and high levels of variation as to who is responsible for making the decisions in each locality.*
>
> TIM deGAVRE

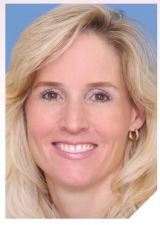
Following this document's release, there was a national and regional stakeholders program launched to encourage the local uptake of biosimilars. In fact, this partnership between the NHS and the BGMA is going to continue into 2016 to actively promote the biosimilar opportunity. The association biosimilar expert sector group which deGavre chairs is entering 2016 with a goal of continuing to partner with patient groups, healthcare professionals, regulators, and NHS commissioners "to increase the understanding and drive a sustainable environment for the development, production, and optimized use of biosimilar medicines in the U.K.," deGavre says. He also stresses the importance of conferences for furthering industry education as the biosimilar market advances. In particular, he cites The European Biosimilars Conference, which will be taking place in London on April 28-29, 2016. "The BGMA will ensure the U.K.'s participation in the upcoming conference, which, in turn, will enhance the nation's focus on building the biosimilar market," deGavre says.

TECHNOLOGY WILL CONTINUE TO DRIVE EFFICIENCIES IN CLINICAL TRIALS

ED MISETA Executive Editor @OutsourcedPharm

Advancements in technology will continue to propel efficiencies in clinical trials in 2016 and beyond. That is the main takeaway from four experts I interviewed who shared their insights on trends expected in the clinical arena. Companies are continuing to turn to risk-based monitoring (RBM) to identify risk and leverage source data verification (SDV) where and when appropriate. Sponsors and CROs are increasingly turning to electronic health records (EHRs) and electronic medical records (EMRs) to identify potential patients for inclusion in clinical trials. It also seems 2016 and 2017 may well be the years that more companies finally begin to routinely incorporate mobile technologies into their trials. Any way you look at it, technology is quickly moving front and center in the effort to simplify, shorten, and bring down the cost of clinical trials.

To gather industry insights for this article, I spoke with the following individuals:



ANNE WHITE
VP, Portfolio Management, Eli Lilly

CORSEE SANDERS
SVP and Global Head of Product Development Clinical Operations and Industry Collaborations, Roche and Vice Chair of the Board, TransCelerate

JONATHAN ZUNG
VP and Head of Global Clinical Sciences and Operations, UCB, and Chair of TransCelerate BioPharma Operations Committee

JAMES J. GILLESPIE
CEO, Center for Healthcare Innovation

TRANSCELERATE DRIVES RBM ADOPTION

RBM IS NOT NEW, but based on the amount of coverage it has received in the last 18 to 24 months, you would think it is currently the hottest trend in clinical trials. Although the idea for RBM was introduced in concept papers and guidance by the FDA and EMA (European Medicines Agency) years ago, it wasn't until TransCelerate released its own recommendations that the industry began to take notice.

"Across the industry, we are now seeing a significant number of studies that are using RBM," says Zung. "We are finally starting to see it become embedded within the industry, and I believe 2016 will be the year we see RBM become a routine part of clinical trials. That is good news for the industry as a whole because it means we can move on from the days of companies sending CRAs (clinical research associates) to sites to perform 100 percent SDV. Going forward we will be using a lot more predictive analytics and data analytics to look at the data in near real time and in a more risk-based fashion, thereby mitigating the number of CRA visits."

Sanders, who also serves as vice chair of the board for TransCelerate, agrees. "This is a concept that has been around for many years, but for it to really gain traction and start moving, we needed alignment at the industry level," she says. "Without that, it would have had a low chance of working."

While RBM may be a blessing for companies and sites, proper change management will be required to get all employees on board. You may already have heard stories about CRAs concerned about how their roles will change or potentially be eliminated as a result of RBM implementations. Zung believes those concerns are unfounded as he sees this as a natural evolution of the CRA role.

"If you look at the companies that are managing this transition well, you'll see they are not getting rid of people in those roles; they are simply changing processes and evolving roles. Many job functions performed by CRAs are different today than they were 15 years ago and will be even more different in the clinical trials of the future. Rather than eliminating head count, many companies are taking employees and simply repositioning them to other areas where there is a need."

Implementing RBM will require companies to perform some activities they may not be currently performing, such as more centralized monitoring and more predictive data analytics. Companies that are implementing RBM and doing it well have put focused change-management plans in place and have generally spent several years preparing for the RBM implementation. "If done right, this change should not come to employees as a surprise," adds Zung. "It should be done as a gradual change that everyone is aware of and prepared to undertake."

CAN EHRs SOLVE THE PATIENT RECRUITMENT DILEMMA?

TWENTY YEARS AGO patient recruitment was an issue for pharma. It still is today and will likely continue to be an issue in the future. But one change that many would agree is here to stay is that the old paradigm for recruiting patients is coming to an end. It used to be a sponsor could hire a CRO, the CRO would find sites that would promise a certain number of patients, and you would hold your breath hoping the sites would deliver.

Today, technology has enabled patients to get more involved in their treatments, which has enabled companies to recruit via patient advocacy groups, social media, mobile devices, and the Internet. Increasingly, more and more companies will also be making use of EHRs and EMRs.

"Technology proliferation, especially the growth of EHRs, EMRs, and PHRs [personal health records] has been huge," notes Gillespie. "It all starts with EMRs located within a given institution. Some of these institutions have millions of records. We are also seeing growth in EHRs, which are records exchanged between two or more institutions. Finally, we are seeing growth in the number of health information exchanges. I believe all of these will increasingly be used for clinical trial recruitment."

While all of these records will help find patients to participate in studies, Gillespie believes they will help with retention as well. Analytics, when properly used with these records, can help identify those patients who are also most likely to stay in a trial, which is just as important as the recruiting. But Gillespie also cautions individuals to not discount PHRs. "They are going to play into this as well," he states. "Efforts in this space by Microsoft [HealthVault, launched in 2007] and Google [Google Health, launched in 2008] have not really caused a lot of excitement in consumers. While many thought PHRs would take off, it just hasn't happened yet. But over time I think this will catch on and eventually we will be using those to recruit patients as well. There are still a few privacy and interoperability issues we need to work through, but all three types of electronic records will be the future of clinical trial recruitment."

> *"There is still a technology gap between countries that we will also have to overcome in the future."*
>
> **ANNE WHITE**

CREATE EFFICIENCIES IN TRIALS

IN ADDITION TO INCREASING RECRUITMENT AND RETENTION, EHRs have the potential to reduce the time and cost of clinical trials. According to Zung, work is under way to take data that has been collected by the physician in their EMR and move it directly into an EDC (electronic data capture) system. This will eliminate duplicate data entry.

White agrees. "That is the real future we hope to achieve from EHRs because this whole effort of collecting data, validating data, transferring it, and getting the source documents verified is a huge resource drain for both the sites and for pharma. We will eventually get there; the question is how quickly we can make all of these technologies searchable."

Zung notes UCB will be running some pilot studies in 2016 to better understand how to move data from an EHR into an EDC. Although EHRs have been used to perform site feasibility and better understand where patients and doctors are located, he believes in 2016 and 2017 more companies will leverage the vast information that exists in EHRs and how to better capture and use that data.

White adds that an additional problem the industry will have to solve is the interoperability of proprietary platforms. For that reason, technology issues will prevent some of these records from being as searchable as soon as many might hope. But inevitably, she believes technology will get to the point where it will be able to search those records no matter what software platform it resides on.

According to White, a third-party company with proper authorization and patient approval will be able to go into those records and match up patients with available clinical trials. To better facilitate the process, getting patient approval from the outset should become a priority for physicians and clinics.

"Patients could sign a form indicating they want their records to be searchable for any available trials," she says. "Patients could opt in when they see their doctor, and I believe physicians would be supportive. A recent survey by DrugDev reported that 75 percent of sites would be very amenable to having their records searched for a potential trial matchup."

White admits things can get a bit more interesting when sites have to refer patients to a different location to be part of a study. But for that reason, she also predicts we will see growth in the ability of patients to participate in a trial from their home through digital devices.

CROs will have a role to play as well. "They should try to figure out how they can help identify those patients via EHRs," notes White. "In addition, if they identify solutions that could help sponsors pull that data from EHRs without having the additional interim step of data collection, this would be transformational for the entire clinical trial industry."

As you might expect, EHRs will not be the same across countries, creating an additional hurdle the industry may have to overcome. Sanders adds, "You can have a very generic electronic health record that might then be tailored by each country to what they need. There are also language barriers that will need to be overcome to facilitate searches."

Still, the advantages will be worth the effort. For example, Sanders says looking at biomarkers will be an efficient way of ensuring companies do not enroll more patients than are needed and give companies considerably more control over the recruitment effort. "If a sponsor is conducting a biomarker-driven study, there may be a database already available you can use," she adds. "That will give companies a good indication of how many patients they might expect to see and where those patients are located."

> *When you look at what companies mean by patient advocacy, the definitions can be pretty disparate.*
>
> **JAMES J. GILLESPIE**

PATIENT-CENTRICITY WILL REMAIN A PRIORITY

ALL OF THE EXPERTS INTERVIEWED indicated patient-centricity will remain a high priority for pharma companies in 2016. For most companies, this will involve working with patients and patient groups to get their perspectives integrated into the trial-planning process.

Gillespie refers to the whole movement as empowering engaged patients. This movement has been happening throughout the healthcare system and is now crossing over into clinical trials. The primary factor driving the trend is actionable information becoming available to patients. There is more information available to patients regarding doctors, diseases, support groups, and of course clinical trials. Along with the additional information comes improved decision making on the part of patients, who now have a greater influence in the process.

"This is a major reason why we are seeing CROs and sponsors creating chief patient officer positions and including them on the executive team," he says. "A review of the media sources covering clinical trials will reveal numerous articles on making patients a part of the planning process. Even consultants are jumping on board with it, and I think that movement is sure to continue into 2016."

Still, for all the discussion about patient-centricity, many companies are hiring a

patient advocacy officer for the first time. As a result, there is still a lot of discussion about what the term patient-centric actually means and how companies can best bring the patient voice in house.

"When you look at what companies mean by patient advocacy, the definitions can be pretty disparate," notes Gillespie. "For some, any process, procedure, or change that makes a clinical trial process more patient-friendly is patient-centricity. It's almost like achieving quality by design (QbD) on the patient side. But for others, that is not patient-centricity at all. For them, patient-centricity might mean actively speaking to, and receiving feedback from, a patient. That feedback can relate to the design of trial protocols and the conduct of each phase of the trial process."

According to White, the patient-centricity movement will benefit patients but will also play a key role in helping pharma companies to get their medicines to market faster. With the problem of low patient participation expected to continue in 2016 and beyond, this effort will be a key step in increasing enrollment rates.

"When we have a new protocol design, especially one in a new disease state, we model it at an investigative site before it is finalized," she says. "Patients and coordinators can then walk through the protocol to make sure it is feasible. It's a great way to make protocols simpler and eliminate unnecessary burdens on patients. If you don't perform that step, you may not find out until the trial is under way that patients are unable to fit the requirements into their schedule. If you lose them at that point, it is counterproductive to both the patients and the trial."

White agrees true patient-centricity means getting patients more involved in trial design. Aside from patients themselves, she believes the person who is best able to tell you what is doable at the site level is the study coordinator. Reaching out to those individuals for input, as well as patients, is one of the best ways to create patient-friendly protocols.

"This input must be received at the study-design level," notes White. "If you start incorporating it after the protocol is finalized, you will have to go through the amendment process, which is cumbersome. If you want even better feedback, have patients read your protocol and provide input into whether or not it is doable. This feedback is especially valuable when it comes from patients who are knowledgeable about clinical trials or have participated in one in the past. I have found many patients to be quite helpful and savvy. These patients will provide great advice on how to make sure you can answer the research questions while not unduly burdening patients."

Sanders defines patient-centricity as working with patients to understand what their burden will be and then acting to properly address those concerns. This can take place from the trial planning process right up through the conduct of the trials themselves. Sanders believes the industry working together, in a manner similar to what TransCelerate is doing in other areas, is the best solution. By sharing experiences and coming up with some common practices for how companies can make patient participation in trials less cumbersome, as well as guidance on how to best implement them, companies can move the process along much faster and make a bigger impact in the lives of patients. We may also be able to engage patients who otherwise would not have considered participating in burdensome clinical trials. Finally, patients can provide invaluable input to protocol development and operational design.

MOBILE TECHNOLOGIES ARE READY FOR ADOPTION

ALL OF THE EXPERTS I INTERVIEWED were upbeat about the prospect of mobile technologies finally making a big push into clinical trials next year. "I think these technologies will play a big role in keeping patients involved in trials," says Sanders. "However, I believe that to be truly successful, the treating physicians must gain a greater level of comfort with these technologies."

Sanders believes many physicians still like to see, hear, and speak to patients in person. When you try to introduce technology that might sever that personal connection, there will be some trepidation and concern for the patient's welfare. For that reason, some adoption efforts could be viewed as additive, meaning they are performed in addition to, not in place of, what was already being done.

Gillespie concurs that physician adoption will be an issue and sees it as a generational problem. "Younger physicians will tell you they love the new technologies, they love emailing their patients, and they like it when patients come in with their mobile devices. You do not see that level of enthusiasm in the older doctors," he states.

Zung adds that these technologies have great potential, especially when it comes to eliminating paper. "Mobile technologies enable patients and sites to collect more data off a tablet or smartphone versus paper," he says. "During the next few years more mobile technologies will be used and less paper will be used in trials."

Today it is difficult to predict what mobile and wearable devices will look like in the future, but Zung predicts that in three to five years a significant number of devices will routinely be deployed in clinical trials to collect data and then move the information from the patient collecting it right into a data system. "There will be a direct link so we no longer have to go through different systems to collect that data," he adds.

Direct data entry is also a hot topic at Lilly. White notes doctors and nurses having the ability to walk around with their tablet will greatly simplify the data collection process. Although this trend is gaining traction in the U.S. and Western Europe, in other areas of the world it is still rare to find sites with tablets or even computers in every room.

"There is still a technology gap between countries that we will also have to overcome in the future," she says. The good news is that EHR adoption might step up to fill that gap. EHR adoption will be pretty far along in many countries, because having electronic records is just a very basic way of running a health network. If that's the case, we can jump past some of these intermediate data entry solutions and get directly to the benefits of EHRs. That would truly be a good vision to have."

Escalating Opportunities And Challenges In Drug Delivery Via Device

DOUG ROE Executive Editor

Everyone is enamored with biologics these days. With the potential to address many unmet medical needs, it's no surprise analyst firm EvaluatePharma is projecting biologics to represent 50 percent of the world's top-selling drugs by 2020. But what a lot of people overlook is that in addition to already arduous development and formulation processes, biologics require a vehicle to deliver those therapies. While biologics are not the only drugs to be delivered via device, their rise in the life sciences industry does focus attention on a broader issue — the convergence of the drug and medtech industries. And with that convergence come many challenges, some of them unexpected.

The following are five key drivers for a successful combination-product strategy:

1 Regulatory

Navigating two different regulatory landscapes, one for drug and one for device, is the current reality. The FDA's Center for Drug Evaluation and Research (governing drugs) and the Center for Device and Radiological Health (governing devices) have different and often conflicting guidance. Identify which regulations apply as early in development as possible.

2 Reimbursement

The Affordable Care Act (ACA) has mandated "increased value" as a determination for reimbursement eligibility. The days of the next "me-too" drug are gone. Leverage the features and benefits of a delivery device to outperform some of these concerns.

3 Patient Compliance

An evolving and empowered patient makes adherence and compliance an ever-moving target. Delivery devices, engineered using human factors design, address needs for tech-savvy patients who have a growing expectation to review their data, understand their diagnosis, and choose their therapy.

4 New Treatments

Treatments requiring a large dose or a larger volume of a drug demand enhancements to delivery-device design. Proficiency in material and mechanical limitations

will fast-track these improvements. Diseases with extreme targeted-delivery needs will necessitate new device innovation. Understanding or overseeing device development timelines can ensure final combination product speed-to-market.

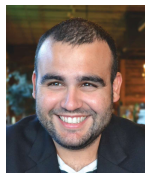
5 mHealth

mHealth and the so-called Internet of Things (IoT) change the future stakeholders in diagnostics, prescription, delivery, and data capture. Who owns, views, uses, and governs the data is still undefined. The IoT creates additional dependence on layers of connected health devices and equipment, as well as the systems to manage it all. The migration from the clinical setting to home health requires a change in the overall approach to a drug company's IT infrastructure, allowing it to operate in this new environment.

These drivers are not project milestone hurdles, but product development considerations. To be a leader in the biologics future may require a change in company culture. The common drug development process can lead to shortcomings when a delivery device is sourced only after drug completion. Even in progressive drug companies that are now designing proprietary devices, the drug and device groups typically are siloed until the drug is in the final stages of development. This historical afterthought approach will not achieve the most effective product outcomes. Early integration of delivery device expertise and methodologies — to create a true combination-product team — will emerge as a best practice in companies that succeed.

I sat down with a group of industry experts to discuss a variety of issues regarding combination devices and how they will affect drug delivery via device in 2016 and beyond.

What therapeutic areas related to drugs administered via a delivery device will represent the biggest opportunities in 2016-17?

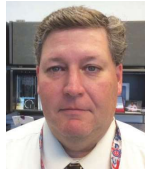


David Amor, *Managing Partner, MEDgineering*

With the FDA approving Afrezza — an inhaled form of insulin — in October, it is a sure bet that similar options will emerge in 2016 and beyond for diabetes management.

Neil Cammish, *Technical Director, International Device Solutions*

Areas related to drugs that are difficult to deliver manually. They fall into two general categories: long-acting release therapies and viscous drug products. For these reasons, rheumatoid arthritis and type 2 diabetes have the biggest opportunities in the short- to midterm. Of course, this will be exacerbated by any related patent expiry.



Chris Eustace, *VP Quality Device Operations, Hospira*

On the oncological side, dealing with cancer, one area will be targeted therapies (acting inside the cell), as opposed to more general treatment (acting on the cell or outside the cell). I think the findings are showing that new advancements in targeted therapies, like signal transduction inhibitors, are actually becoming more effective than conventional chemotherapy. I am not sure about next year. It might be a little further out in 2017. But any time you can go directly at the area that is affected, it is a much cleaner application than whole-body therapy.

Olaf Queckenberg, *Head of Global Chemical and Pharmaceutical Development, Bayer Pharma AG*

Therapeutic areas with a high share of biologics, like oncology, immunology, hematology, neurology, ophthalmology, and diabetes (insulin) are likely to see the biggest increase. Some of these therapeutic areas require chronic treatments where patient adherence is key. Reduced dosing frequency, patient self-administration, and improved convenience are important aspects in development, which can be addressed by innovative formulations and delivery devices.

Anand Subramony, *VP Drug Delivery & Device Development, MedImmune*

Clearly rheumatology and other inflammation diseases. Asthma is an area where there is going to be tremendous value created by device delivery features that make a big impact on patient-centricity. Another area is lupus, which is going to have some novel devices come into play.

Which drug delivery device platforms do you expect to have the most growth in 2016?

Amor: Inhalers are an area seeing significant disruption. Intranasal administration routes are gaining popularity. Drug manufacturers are trying to figure out how to use drugs with an inhaler platform for faster and more efficacious delivery.

Teva recently purchased Gecko Health, whose smart inhaler has a sensor that enables data analytics for chronic disease management on a mobile application. I expect that pharma will continue the acquisition trend of targeting mobile health products and technologies to enhance their current delivery device portfolios.

Cammish: There will also be large, mostly hidden, growth in device development for bolus and high-volume delivery mechanisms. This is mainly due to latency in the market and the start of second-generation me-too devices, which will add additional patient benefit and market advantage. Think of the smartphone leap from the functional entry-level Windows CE phone (in 2001) to the dynamic iPhone (in 2007) we know today.

Eustace: A bigger part of therapy will move toward transdermal drug delivery, things like the patch and advances in microneedles.

I don't think you are going to see much on the infusion side. With the current

focus on cybersecurity, the regulation evaluations and the new requirements that will be defined are putting delays on product development. The "smart pump" is probably a few years away.

Queckenberg: Drug-delivery devices for injections will see the largest growth, along with smart auto-injectors with software functionalities that help patients to manage their disease and apps that offer the possibility to read data from the device, as well as enable patients to track their drug intake and facilitate the exchange of data with healthcare professionals. This will become the new norm.

Digital health solutions, such as medical software, smartphone apps, sensor technologies — alone or in combination with delivery devices — will be a fast-growing segment in all disease areas and application routes. They will help patients and physicians to better manage disease and to adjust medical interventions to the needs of the patient.

Subramony: We are going to see a lot of innovation in the prefilled syringe (PFS) space. We have some forms of PFS in the market now, but what I think we will see is more robust designs, improved safety mechanisms, and needle retraction.

Auto-injectors will continue to be a key product. Much of this is patient-centered, moving the treatment from hospitals to homes. It is all about providing the medication in the safest way, with minimum pain, and in a convenient fashion. There's also a good chance we will see some large-volume auto-injectors and bolus injectors next year.

Stephen Wilcox, Ph.D.,
Principal & Founder, Design Science

We are at the beginning of a revolution — the IoT — that is going to change everything. A simple example would be a sensor that is part of a connected device. It is recording and tracking behavior that is saved to a database. That data can serve many functions. Patients can access it to see how they are doing, physicians can access it to monitor adherence, and the system itself can evaluate the data and send a reminder to the patient to aid in compliance. Now, imagine many of these devices and databases all interconnected. With that volume of information about a patient, it transitions from just monitoring to diagnosing and, eventually, prescribing. With that system of connectivity, a physician could interpret and prescribe the appropriate medicine, which would then automatically be loaded into an infusion pump. Delivery platforms will become part of a larger system we call product service ecology.

What will be some of the key challenges facing companies that are expanding competencies into these delivery device platforms?

Amor: The key challenges are less about the technology itself and more about the integration of two distinct worlds — pharma and medical device. Quality and regulatory requirements in each industry are slightly different, and often the biggest challenges emerge when companies aren't aware that the constituent products of a combination product are also governed slightly differently. Although the FDA's cGMP rule for combo products (21 CFR Part 4) was released recently, companies are still struggling to apply it to their new drug-delivery submissions. Companies that are committed to drug-delivery device products must also invest in a robust regulatory/quality system that streamlines submissions and ensures compliance with new regulations and standards.

Cammish: There are challenges to multiple groups: *R&D* — Finding an unmet need related to the combination of drug and device. *Legal* — Not losing sight of intellectual property considerations. *Human Resources* — Sourcing experienced staff and expertise that have both technical and industry device experience. *C-Suite Leadership* — Trusting the device experts that you hire.

Eustace: Understanding and navigating through the regulations will be a key challenge. Regulation clarity is a big issue with the FDA, and that challenge expands as you consider your international markets and the corresponding regulatory bodies. Each is, at best, slightly different.

It may be a variation on the question, but leveraging your full company capabilities after a merger also is a challenge related to delivery via device. You have a new mix of drugs and delivery devices. Identify which ones offer the most effective, and potentially new, combinations. Often this is a driver for the merger, but taking time to evaluate your combined pipelines could lead to a major opportunity.

Subramony: Build vs. buy is a key debate that many companies go through regarding device development. Pharm/biotech often face the challenge of how much in-house device development to undertake. Building internal delivery device platforms certainly can help address product readiness and time to market. However, several key competencies are required to grow in-device platform development. For instance, in addition to core mechanical engineering and design expertise, you also need human factor engineering expertise. Platform development is a cross-functional activity in which areas/functions like drug substance and formulation must be considered early on. Understanding the regulatory landscape for combination product development throughout the platform development cycle is very important.

If you are vertically integrated, you can build the device capability as a core competency within your company. The insulin market is an example. The device drives your product differentiation, so you build the device strategy around it.

If you have differentiation in terms of efficacy or novel mechanism of action, a device could bring you additional "best in class"status through patient-centric features. Even for this scenario, it is best to integrate device development early on in product development.

Companies also need to understand how payers are going to view one delivery solution over the other. It has to be part of the overall product development strategy from Phase 1. No longer can you wake up before Phase 3 and find a solution.

Combination Product Devices

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Wilcox: Do pharma companies have the skills needed to manage/handle/address connected health considerations? System and software engineers will be a requirement. Also, database development and database management will take on a much greater importance, as companies begin to capture and analyze the large volumes of corresponding data being created.

How can drug companies drive innovation in delivery device design in 2016 and beyond?

Amor: Human factors engineering (HFE) ensures that adoption of novel delivery platforms will be successful. Users and caregivers in many therapeutic areas are used to a drug-based treatment regime; introducing a new "toy" that changes administration can be a scary proposition. Usability studies and HFE work should aim to allay these anxieties and understand use cases, not to mention the FDA is requesting HFE work in combo-product submissions. Out of the last four combo-product submissions I have directly worked on, three of them contained HFE questions in the first round of review.

Cammish: Install user-led design. Focus solely on delivery mechanisms and devices, without waiting for a molecule. Funding is typically top-down therapy-led, with a direct market need and an aggressive timeline. There is a definite innovative benefit to stepping back and funding development outside of standard project constraints. Determine what patient populations require and work from the bottom up. The allocation of time and space for existing device-development teams, working only on innovation, is what would be required.

Eustace: The reason most companies struggle with innovation is because they don't understand the differences — and potential similarities — between the two sides of the business (drug and device). They don't talk to each other. There is a wall that is built up. Part of that wall is the distinct quality systems. Things are too different on each side. Installing one companywide quality system would bring the partners together early in the development cycle in order to coordinate the entire combination-product requirements. Then, you keep the teams together for the R&D process. Having them together will build a bridge between the differences and will lead to them discovering opportunities.

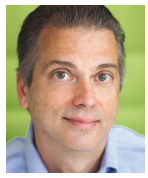
> "Expect double-digit growth in auto-injectors and other devices capable of high volume and/or viscous drug delivery. The majority of this growth will be linked to biologics."
>
> NEIL CAMMISH

Paul McKenzie, Ph.D.,
Head of R&D, Ethicon
To provide the best possible device solutions for the patient, we have adopted an open approach with our device partners. By sharing our requirements freely with device developers, and de-emphasizing the need to control IP, we have been able to help promote the development of innovative designs.

Subramony: There is a lot of opportunity to advance patient compliance. Improving assurance (safety) and designing with a human factors approach should be main considerations. The goal should be to grow expertise in device design.

Don't just rely on your internal expertise alone. Reach out to design companies and explore the whole idea of tech disruption. We work closely with such companies. Identify if you have the right experts in your organization and if you are building those unique competencies internally. Or, determine if you need to implement an external approach to have your people learn and grow.

Wilcox: Companies need to take a holistic approach to the patient-therapy life cycle and incorporate an understanding of all the interconnected products, software, and systems that will be involved. Then, innovation will come from how a solution can best be integrated.



Rob Willenbucher, M.D.,
Head of Cell Therapy, Janssen R&D
Enhancing the experience for both patients *and* healthcare providers is a key driver for device innovation. We have broadened our approach to focus not only on the device but also how it is used and the human factors that may impact the entire procedure. These considerations include both the physical and cognitive workloads associated with using the device. We have demonstrated positive results applying both human factors and industrial design expertise to a cell-based therapeutic with a fit-for-purpose delivery system.

What are your market growth expectations for drugs delivered by device?

Cammish: There will be little growth in pen devices as therapies shift to longer-acting, modified-release drugs. It is not that the usability or utility of the pen injector will decline, but simply a reduction in its frequency of use.

Expect double-digit growth in auto-injectors and other devices capable of high-volume and/or viscous drug delivery. The majority of this growth will be linked to biologics. The core need is for patient convenience, coupled with the reduction of clinical care costs by facilitating home use.

Subramony: It is definitely going to be a market with tremendous growth, next year and beyond. Because of the growth in biologics, the research data is pointing toward device-based combination products overtaking oral as the prime delivery method. L

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IN 2016, Can Outsourcing Relationships Survive The Biopharma Life Cycle?

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CEO, Ono Pharmaceutical

When I ask about the future of outsourcing, I get talk of relationships. Firelli "Fi" Alonso-Caplen, senior director, biotherapeutics and vaccines outsourcing at Pfizer, even mentions the "m" word. "There's no perfect CMO. Neither is there a perfect client! Both have to work at cultivating a harmonious relationship. Both have to own it — no finger pointing when trouble arises. It's less of a business-driven outsourcing contract and can only be accomplished over time. Like a *marriage*, it takes two to have a successful relationship, and therefore celebrate many anniversaries."

To sponsors around the world looking for enhanced outsourcing outcomes, and for those looking for improvements at service providers, Alonso-Caplen's words are enlightened. For years now, there's been a focus on improving the sponsor-provider working dynamic. All of the industry experts (from Bayer Pharma AG, Capricor Therapeutics, Pfizer, Shire and Ono Pharmaceutical) I spoke with for this article on the future of outsourcing mentioned improving relationships. I'm sure many readers have your own thoughts on the subject; those of us covering the industry have certainly written our share on this theme.

But that is where we are *now*. Aren't there new and larger paradigms to divine beyond improved relationships and partnerships when contemplating a *future* for outsourcing in the biotechnology and pharmaceutical (biopharma) industry? How about something more comprehensive to better guide the industry through times of thick and thin, economic ups and downs, or disruptions of innovation and regulatory change? Maybe these cycles themselves are a clue.

I Want More Than A Relationship

Over decades now, outsourcing has become tightly intertwined with the broader biopharma industry. Today it has become, if you will, a better union. They do share a similar future. David Lowndes, SVP supply chain management at Shire Pharmaceuticals, makes the point simply: "I expect outsourcing to continue to grow as we grow our business."

Numbers demonstrate that growth. Various industry analyses currently peg

the combined annual discovery and CMC (chemistry, manufacturing, and controls) outsourcing spend at somewhere approaching $40 billion. Whatever the exact figure, what's clear is that effective outsourcing has become essential for profitable drug development and manufacturing strategies at a growing number of companies. Moreover, outsourcing itself is increasingly a bona fide *business* model, serving as the organizing principle for startups and their investors. The "one C-corp-per-compound" model of a startup like Dauntless Pharmaceuticals in San Diego is an example. There are much bigger examples as well; the majority of products in Lowndes' global supply chains at Shire are outsourced. Even a historic company like Ono Pharmaceutical in Japan has no facilities of its own for API manufacturing. These are more than strategic relationships with service providers; they are *modi operandi* — fundamental methods of operation.

This is not to put forth an industry forecast of all outsourcing all the time. Bayer Pharma AG's Stefan Jaroch, head of external innovation technologies, global external innovation and alliances, says, "While outsourcing will remain an important part of our drug discovery and development, we do not necessarily see a rise in the quantity of work outsourced, but instead, a different quality of working with outsourcing partners. For example, we're involving CROs more deeply in developing and testing compound syntheses in our discovery programs, instead of just approaching them for one-off synthesis projects."

Alonso-Caplen concurs. "At Pfizer, we rely on outsourcing mainly to supplement any need for capability or capacity. For example, our manufacturing strategy remains to produce in-house first, particularly with complex projects in the pipeline. At the same time, I believe outsourcing will continue to increase, particularly when new biological modalities arise, as in antibody-drug conjugates and cell and gene therapies."

The point here is that in 2016 and beyond, *how well* everyone from Big Pharma to virtual companies outsources is the real measurement of success, not necessarily how much. But while both quantitative and qualitative increases in outsourcing will rely on more enlightened relationships as a key component, the future of outsourcing — and thus an increasing part of the future of all biotech and pharma — can't stop there. In fact, while perhaps still couched in the language of relationship-speak, industry professionals are broadening internal themes and thinking in paradigm shifts in an effort to move the outsourcing industry to a much greater maturity. Let's take one more step back before diving into these new ideas.

Existential Outsourcing: We're In This Together

Biopharma industry experts start by walking me back to where we've come from before moving to thoughts of the future. If you don't know your history, you're bound to repeat it.

The narrative often starts with the recession of 2008, a period when the global economy and stock markets tanked, the "new-drug pipeline cliff" was an obsession, and customer projects dried up at CROs and CMOs. This also led to a period of heightened emphasis on pricing. CROs and CMOs were now just cost centers: the less money out, the better. An intensifying globalization of outsourcing added to those pricing pressures — as it always does in any industry. But there was more to it than that. The new view of outsourcing was as a cost-cutting component within a businesswide and intense focus at sponsors to cut expenditures during an uneasy economic period.

However, the results from emphasizing pricing were uneven and raised questions. Was it helping to advance pipelines where future revenue resided? Were quality and risk increasing in the supply chain? Partly in answer to these questions — as well as a modestly improving economic outlook in general — the pendulum has swung to the other side, bringing us to the modern mantra of relationships over transactions. Providers still need to deliver a competitive price, but today the dialogue centers on developing strategic outsourcing partnerships.

"In my opinion, today there is no reason why outsourcing should represent a more risky option for your supply chain, if you carefully select the right partners," says Lowndes of Shire. "Your expectations should be the same as if it were internal manufacturing. Crucially, it has to be a win-win: the CMOs also need to meet their business goals for this to be a sustainable business model."

Accomplishing that win-win equilibrium — and specifically that sustainability — will require a new component of vigilance and guidance through times of both internal and external challenges to sponsor-provider relationships. Here are some current examples of those challenges:

When the iShares Nasdaq Biotechnology Index (IBB) drops 25 percent in a quarter as it did in Q3 of this year, biotech service providers hear a loud bang. Which customers of theirs might tighten budgets, cut programs, or within an elongated downturn, face existential risk?

When politicians browbeat the pharmaceutical industry on commercial pricing for innovative drugs and threaten to enact less-than-logical legislation, service providers brace for tougher negotiations with sponsors. Will relationships save them from intense pricing pressures this time around?

And when the Trans-Pacific Partnership Agreement (TPP) for international trade hinges on negotiation of IP protection for biologics and the timing of biosimilars to enter markets, some in the outsourcing industry revisit their five-year business plans. Will global affairs increasingly send waves of concern over service providers?

The future state of outsourcing, then, has a lot to do with ... well, a lot. And attitudes, economies, markets, companies, and products — and science and technology itself — all work within their respective life cycles. And come to think of it, what is more familiar than life cycles to the biopharma industry?

Coexisting In Life Cycles

The world of biopharma understands its pipelines, products, markets, and

patients in terms of their respective life cycles. Our biopharma executives are as attuned to broader economic and business cycles as those in any other industry. The suggestion here is to apply this understanding more directly and rigorously to outsourcing. More precisely, the life cycle of an individual drug discovery or development program or franchise, a business unit or entire company business-model, or more macro spheres like national or global economies becomes the guiding principle of interaction and communication between outsourcing companies and their service providers.

Bayer Pharma's Jaroch explains that before embarking on strategic outsourcing, for example in research, "the CRO's *client* needs to define precisely which value generation it expects from the CRO at that point, and which work packages are best suited to be pursued by the CRO at that time. The client has to define whether it is at the point of needing just capacity to enhance its flexibility in resource allocation, looking for access to specific technologies and capabilities, or being interested in bundling resources with a CRO to share risks."

In fact, if you listen closely, you start to discern the advance of the life cycle arc in the comments of various executives. Denise McDade, VP of quality at Capricor Therapeutics and whose career has spanned positions at companies such as Genentech, Novartis, and Amgen, says she's learned it's best to let your service provider know exactly where you are in your product and entire business life cycles. "Some decisions get made for you simply by where you are as a company," she says.

For example, Capricor was formed through a reverse merger in which it inherited an existing peptide product that was in the clinic and outsourced. "It was a no-brainer to keep that outsourcing model for that product," says McDade. "I believe it will always remain outsourced." If information like this on the outsourcing life cycle plan is openly shared with service providers — not always a common practice today — we may get to a win-win for both sides ... and the ability for both sides to understand risk and weather any life cycle forces that might buffet the trajectory of a drug development program. McDade continues: "We also have an internal product nurtured by ourselves in clinical trials. The manufacturing process is complex and strategic for us, and we've kept it in-house. When we commercialize this product, do we want to outsource manufacturing? We're in the middle of answering that, and our partners should know clearly where we are in terms of that whole process."

> "Leasing a suite, say for a year if there are several projects, might be the better strategy for outsourcing."
>
> FIRELLI "FI" ALONSO-CAPLEN

Lowndes speaks further in terms of transparency. "Shire and our partners operate as if we were one company. We work together to drive process capability and quality by exchanging process data each day and jointly reviewing performance to drive action. This has delivered significant improvements in process capability, quality, and supply performance, yielding benefits to both Shire and our partners. Apply the same standards and expectations to yourselves and your CMOs that you would if it were a vertically integrated model. The only difference should be who owns the facility!"

Alonso-Caplen has considered advanced approaches to her outsourcing. "The stage of R&D maturity in a specific area might call for a kind of 'lease strategy,' for example potentially with cell and gene therapy," she explains. "There's an increasing demand for CMOs in this landscape because of more early signs of efficacy in the clinic. Since currently the majority of these projects are small-scale, correspondingly small cGMP modular suites using single-use systems are being built to meet this demand. Leasing a suite, say for a year if there are several projects, might be the better strategy for outsourcing. It may not necessarily be cheaper in the midterm, but it might be the better approach to meeting tight timelines in this arena."

We mentioned above that Ono operates with no API manufacturing facilities. CEO Gyo Sagara tells me that for the past few years Ono has also focused on finding ways to utilize resources outside the company earlier in the drug discovery and development life cycle. Sagara and Ono have come up with a new paradigm in which outsourcing per se is subsumed. To describe this — and ensure it is enacted upon — Ono has coined the term, "Orientem Innovation," taken from the idea of a holistic "therapeutic-area oriented" approach. Sagara says this is an "open research network" targeting future partnerships with academia and including outsourcing collaborations as needed. "Outsourcing should be seen as providing complementary solutions along the product continuum, as an integrated part of a business' continuity plans, and as a function of an overall business plan," he says.

What Will We See In 2016?

As we know and have discussed here, in the biopharma industry, those business plans Sagara mentions above are contemplated with various life cycles in mind. Perhaps all we have been saying then is that in 2016 and beyond, while the trend to improve and expand outsourcing relationships remains important and (hopefully) positive, those relationships can't reach their full potential without a shared and full understanding of the timing and times within which they exist. The professionals quoted in this article — and so many others around the globe — are entertaining new concepts for approaching outsourcing. For lasting success, they must include some form of win-win even in times when some life cycles are on the decline. Let's see which new paradigms are introduced in 2016 and which ones we'll be talking about much further into the future.

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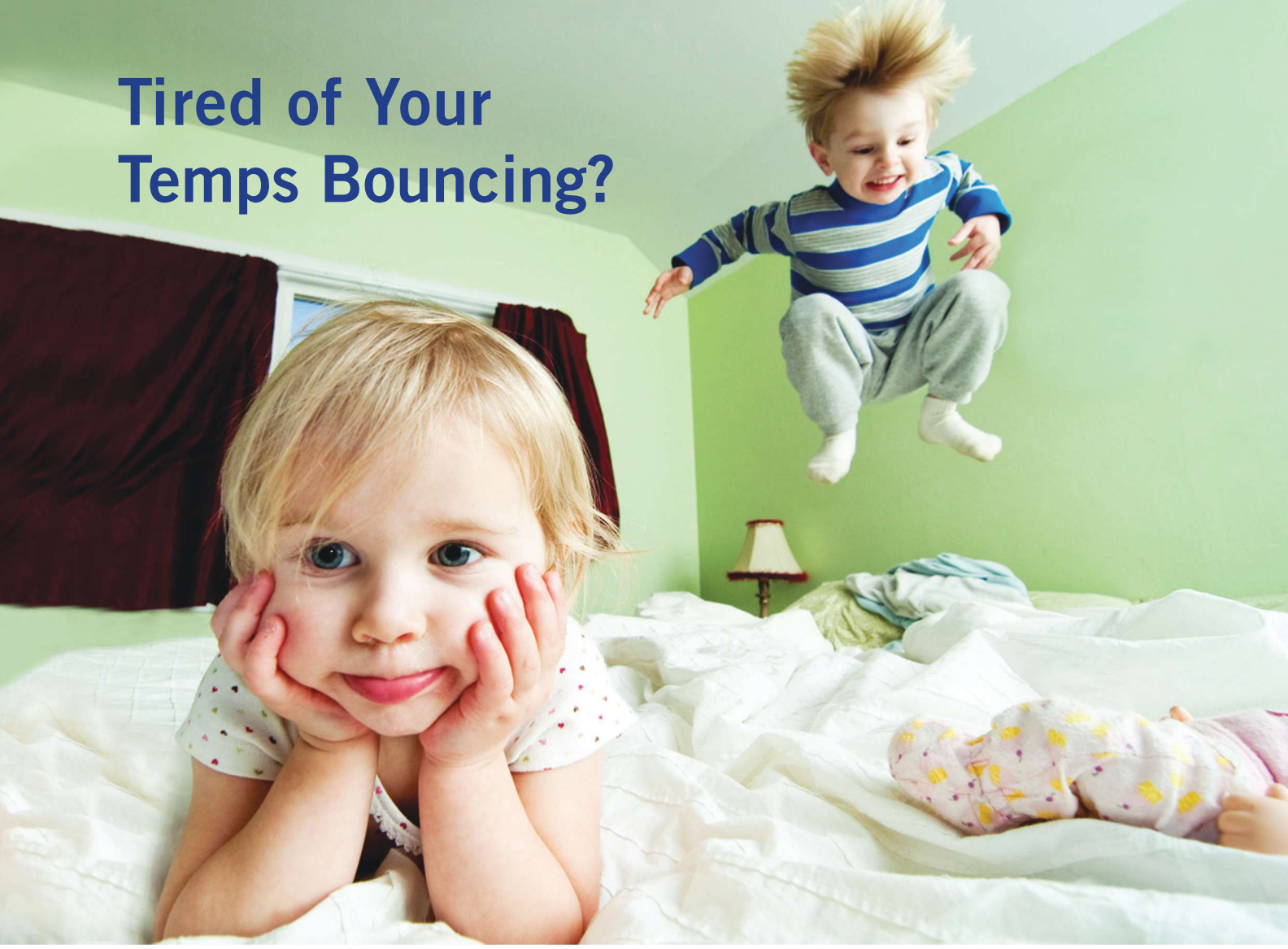

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AGILITY & FLEXIBILITY

To Drive Pharma Manufacturing In 2016

KEN CONGDON Executive Editor @Ken_Congdon

As pharmaceutical manufacturing continues its shift from a volume-based business to being more specialized, pharma companies are attempting to reinvent themselves in this altered, and sometimes unfamiliar, landscape. While many core production objectives remain the same (i.e., bringing new therapies to market, maintaining GMP, ensuring quality assurance, and meeting supply demands), the means by which to accomplish these goals are more multifaceted than ever before. Therefore, as pharmaceutical companies enter 2016, they need to focus on making their operations more agile and flexible.

The pursuit of enterprise agility in pharma isn't a new concept. It's been a key topic of conversation at industry conferences for the past several years. However, many key stakeholders of manufacturing, quality, and supply chain efforts are calling 2016 "The Year of Agility" in pharma. To these leading minds, the trends that will have the most impact on the pharmaceutical sector in the coming year are either a direct result of this quest for added flexibility or will place added emphasis on the need for enterprise agility.

Pharma Consolidation Requires Facility Rationalization

M&A activity in the pharmaceutical sector was intense in 2015. It is estimated there were $221 billion in deals in the space during the first half of the year — three times the amount realized in the first half 2014. Among the biggest deals were Pfizer's acquisition of Hospira for $17 billion and Teva Pharmaceutical's purchase of Allergan's Generics Division for $40.5 billion.

Most industry thought leaders expect this M&A activity to continue in 2016. In many ways, these acquisitions are part of Big Pharma's strategy to become more agile through organizational synergy. For example, mergers allow pharmaceutical companies to inherit mature, proven assets without having to dedicate capital to R&D. They also are a quick way for organizations to secure the infrastructure necessary to enter new lines of business and meet growth objectives.

However, while often thought of as means to become more agile, a merger actually places more flexibility demands on a pharmaceutical organization. "We've seen companies merge that have very different manufacturing philosophies," says Alison Little, advisory leader for life sciences at KPMG. "For example, one company is focused on manufacturing its products internally, while the other invests heavily in outsourcing. In these instances, the combined company needs to rationalize its facilities with an eye on reducing its overall costs and footprint. This involves deciding which plant locations best support the new organization's overall strategy and which should be repurposed."

Realizing a quick return on investment from late-stage assets gained through M&A activity also requires an extremely flexible manufacturing operation. "Following a merger, it's important that the manufacturing and supply chain footprint that exists be able to turn on a dime to support the further development

and commercialization of any acquired late-stage assets in order to have revenue expectations realized," says Pravin Khandare, VP of procurement, Janssen.

> *The advancements being made in continuous manufacturing are amazing — particularly when you consider the modular manufacturing facilities some pharmaceutical companies are creating.*
>
> ALISON LITTLE

Biologics Growth Impacts Scale

The pharmaceutical industry has historically been one built for volume. Manufacturing facilities were designed to efficiently churn out mass quantities of blockbuster drugs aimed at treating common conditions. This dynamic is changing. In recent years, an increased focus has been placed on specialty medicines and biologics aimed at rare diseases and smaller patient populations.

According to a June 2014 forecast from EvaluatePharma, biologic products account for only 4.7 percent of total sales in the top 100 drugs today, but they are poised to account for 52 percent of sales by the end of the decade. Similarly, BLAs (biologics license applications) make up more than 50 percent of the global pharmaceutical pipeline, and that figure is expected to grow to 75 to 80 percent by 2020.

"One of the consequences of this shift from blockbuster to specialty drugs is scale," says Little. "Pharmaceutical manufacturers need to learn how to scale differently in a world where volume is no longer the primary driver. Much of the emphasis is now placed on running smaller, more frequent, batches. As a result, pharma manufacturers need to be flexible enough to quickly switch from producing one product to another."

The rise in biologics is also likely to impact production cycle times, because these therapies are more apt to be designated for Fast Track, Breakthrough Therapy, Accelerated Approval, or Priority Review by the FDA. These designations help to speed the availability of drugs that treat serious diseases, but they also place additional pressure on pharmaceutical manufacturing organizations.

For example, in a traditional clinical trial, Phase 1, Phase 2, and Phase 3 are spaced out. As such, pharmaceutical manufacturers have ample time to develop and optimize manufacturing practices associated with the new drug. This helps ensure processes are consistent and reproducible and also gives stakeholders ample time to develop contingency plans. When a drug is fast-tracked, the clinical trial and approval timeline is accelerated, but the medication must still adhere to the same rigorous manufacturing and quality standards as every other product.

"In a fast-track scenario, you have to be ready to launch drugs in an accelerated fashion, which significantly reduces the amount of time a manufacturer can dedicate to process development, adjustments in scale, and stability studies," says Maninder Hora, SVP of pharmaceutical development and manufacturing operations at Nektar Therapeutics. "Because of this, you need to have an all-hands-on-deck approach to manufacturing. You need to accelerate your internal timelines immensely to ensure your processes are ready when the expedited approval is granted."

Continuous Manufacturing, Single Use On The Rise

The need for smaller, more frequent batches of specialized drugs will also impact production strategies in 2016 — all the way down to the way manufacturing facilities are designed. On the small molecule side, this means increased use of continuous manufacturing.

"The advancements being made in continuous manufacturing are amazing — particularly when you consider the modular manufacturing facilities some pharmaceutical companies are creating," says Little. "Unlike the enormous, purpose-built facilities historically reserved for producing large volumes of small molecule drugs, modular manufacturing units are about the size of a standard living room. Furthermore, they can quickly be reconfigured and repurposed to produce different types of medications on the fly. We'll see more pharmaceutical companies embrace this type of flexible manufacturing in 2016 and beyond."

On the biologics side, the trend isn't continuous manufacturing — it's increased reliance on single-use technology. "As the industry moves toward higher-affinity proteins, smaller patient populations, and lower overall volumes, single-use disposable technology becomes more prevalent because it efficiently addresses small-scale demands," says Lance Minor, VP of network strategy and business operations at MedImmune/AstraZeneca. "With single use, you have the ability to bring clinical-scale production to your commercial market for these low-volume products."

> *We have been placing more emphasis on shadowing the systems and operations of our outsourcing partners.*
>
> MANINDER HORA

For pharmaceutical companies like MedImmune/AstraZeneca that produce a wide variety of both small molecule and biologic therapies, the shift to smaller, more frequent batches is also expected to have a dramatic impact on demand variability. According to Minor, MedImmune is currently focused on performing more adaptive clinical trials that require testing a broader range of doses later in the development cycle. This approach can create huge swings in clinical demand overnight. To satisfy this highly variable demand, MedImmune/AstraZeneca has placed a premium on building more white space (open or unutilized manufacturing infrastructure) and shorter changeovers into specific sites within its network.

"Operating at less than 100 percent utilization means we may run fewer lots in a year should clinical demand not materialize," says Minor. "To date, our swing

space continues to be filled almost faster than we can free it up through process improvements. Planning for uncertainty with white space is necessary to ensure we are flexible enough to ensure opportunities to advance and accelerate our clinical programs."

Managing Product Diversity, Capacity Requires CMO Support

With the rise of biologics, and even more recently, combination products (i.e., the pairing of a drug therapy and a medical device), the pharmaceutical industry is more diverse than ever before. This environment makes it increasingly difficult for pharmaceutical companies to handle everything in-house. As a result, more and more organizations are partnering with CMOs for support.

"As a midsize company with drug candidates across multiple therapeutic areas and drug classes, it's inconceivable for us to build infrastructure for producing small molecule, biologics, and medical device operations," says Hora. "This puts a lot of pressure on us to outsource judiciously and select CMOs with the required capabilities, capacities, and quality systems. We also must maintain these CMO relationships in a transparent, team-oriented way."

Over the past few years, the accountability for ensuring the quality and accuracy of a prescription medication has shifted from being shared between the pharmaceutical company and the CMO to being more weighted on the sponsor. New regulatory guidelines have been implemented expecting the sponsor to be ultimately responsible for "ensuring that processes are in place to assure the control of outsourced activities and quality of purchased materials." This increased responsibility makes it even more important for pharmaceutical companies to choose their CMO partners wisely and ingrain themselves in the outsourcing operation.

"Because the pharmaceutical company has ultimate responsibility for the final product, we have been placing more emphasis on shadowing the systems and operations of our outsourcing partners," says Hora. "In other words, we are focused on ensuring they are manufacturing our product in a manner that meets our standards without being physically present at their facility at all times or owning their infrastructure."

Coping with increased product diversity isn't the only driver behind the rise in CMO partnerships. This is also a key strategy pharmaceutical companies are using to deal with capacity constraints. According to Minor, MedImmune/AstraZeneca is planning two new product launches a year on top of the already highly variable demand it is experiencing. The capacity issues that arise from this type of environment can often lead to drug shortages. To protect against this scenario, MedImmune/AstraZeneca is leveraging CMO partnerships to shore up capacity.

"Because our product forecasts are uncertain, we're trying to get a better hold on our supply chain overall, our ability to build inventory, and improve our overall capacity through expansion," says Minor. "Our CMO relationships are central to this effort. They help give us the flexibility we need to meet ever-increasing demand."

Supply Chain Visibility Becomes Paramount

Increased reliance on CMOs means pharmaceutical manufacturing supply chains are becoming more and more extended. To ensure inventory, quality, and delivery objectives are met requires improved visibility into this external network.

"As pharmaceutical manufacturers add CMOs to the mix, more of the supply chain gets out of their normal bounds and often out of their line of sight and control," says Khandare. "This introduces new and different risks that must be managed. Enhanced visibility into the external supply chain is imperative to success going forward."

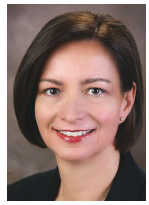
> *With single use, you have the ability to bring clinical-scale production to your commercial market for these low-volume products.*
>
> LANCE MINOR

Determining the source of supply chain risk is a huge area of focus for pharma in 2016. This effort entails knowing where materials are coming from and how they are moving at all times. It also requires contingency plans be developed if there are delays with specific partners or intermediates.

According to Khandare, developing deeper relationships with external partners is crucial to gaining this visibility. "You need to know their shops as well as your own," he says. "This requires collaboration across several different levels and functions — quality to quality, regulatory to regulatory, manufacturing planning to manufacturing planning, etc. This is the only way to make risks visible and ensure you can bridge any gaps. Moreover, this type of collaboration and risk management needs to be done proactively. If it's reactive, then it may already be too late." L

MANINDER HORA
SVP of Pharmaceutical Development and Manufacturing Operations, Nektar Therapeutics

PRAVIN KHANDARE
VP of Procurement, Janssen



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INVESTMENT EXPERTS FORECAST Gains OVER Pains IN 2016

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

This fall, during the weeks following the great Turing-ignited clash over drug pricing and the consequential plunge in biopharma stocks and valuations, we captured the thoughts of six leaders in life science investment capital, which fuels drug development by hundreds of new companies every year. We asked them to look ahead to the new year and tell us, did the downturn signal an end to the boom times in biotech funding, as many believe – or if not, what sort of future for the industry does the changing financing climate forebode?

Our six investment leaders represent a broad complement of firms, varying considerably in size and type, focus, and experience. (See sidebar "The Forecasters.") Each of the participating individuals also has a unique history and viewpoint of the funding landscape, yet all often agree on the big issues affecting the changing climate.

Doomsayers may be surprised. In a word, no – not one of the experts believes the good times for life science funding are coming to an end, even though every one expresses concern for the fate of industry innovation in the longer term. It is in the details that their views diverge and often complement each other.

INFORMED FORECASTS

We first asked the experts for their general assessment of what would follow in 2016 from the October plunge that seemed to erupt with a CEO's defiant pricing strategies and continued with new pressures from political and economic forces. All of them agreed on this point: Despite all, the life sciences space remains strong, resilient, and resistant to prolonged, destructive downturns that would signal another burst bubble.

Where do you believe the funding/ investment environment – from angels to VCs to the stock market – is heading in 2016? Will the "boom times" in biotech financing finally end?

"The idea that we would have unlimited pricing power forever might become more difficult to maintain over time," says Carl Goldfischer of Bay City Capital, a bimodal firm that handles both start-up and late-stage pre-IPO investing. Goldfischer assesses the downturn's long- and short-term effects:

> *The correction we've seen is an ending of a certain type of boom in the sense of multibillion dollar valuations for nonclinical-stage companies. The core bullishness that drove this remains: the thesis that there are too few high-quality, breakthrough novel therapeutic assets to meet the demand. The larger biopharmaceutical and pharma companies still do not generate enough new drugs in their core R&D operations to satisfy the pipeline needs, and to the extent that people like us invest in companies that do make a real difference in disease outcomes, we will still be rewarded handsomely for our work.*
>
> *Coming six months later, when many IPOs are planned, the downturn could have had an even more depressive effect on the sector. IPOs are slowing down, many of them are being pulled, and I believe that environment will carry through for some time. Still, many venture funds have made a ton of money in this space and are flush with capital, but the capital will be pricier and harder to come by. If you're a buyer of assets, you will probably get better entry points, but all the companies with assets to sell will be private companies. If your company is trying to sell a very novel technology at a high price, but at an early stage without much clinical proof, it will be harder to do now.*

Along with the others participating in this article, Goldfischer points to the flight of the generalist investors from life science stocks in the hoopla over pricing in October. Generalists, essentially industry neophytes, were in fact important drivers of the IPO "good times" in recent years. But for the time being, they have largely exited the market via the simple act of selling their bio stocks. Veteran investor Dennis Purcell of the large New York-based firm Aisling Capital, offers a more sanguine take on the sell-off:

> *The recent correction is not that big a deal. It comes after we had five or six great runs, companies are much better capitalized, and we should not see the kind of crisis we had in former downturns. Having said that, we lost about $125 billion in market value during September and October. People say the generalists are leaving, and there's truth to that. I look at the ETFs [exchange-traded funds], securities traded separately but usually rising or falling in parallel to the stock market, and primarily owned by individuals. There were about $20 billion in ETFs, and that went down to between $14 billion and $15 billion in October, meaning individuals were leaving*

THE FORECASTERS – LIFE SCIENCE FUNDING 2016

A broad sample of financing experts from a variety of firms answered our call to envision the funding environment for innovative life sciences companies in the coming year. Two members of the following group rejoin us from the "Strategic Options In Financing Your Biotech" roundtable (October 2015 issue), held at BIO's annual meeting last summer; the others appear here for the first time in *Life Science Leader*.

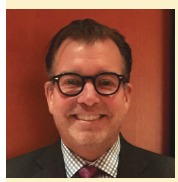
CARL GOLDFISCHER, M.D.
Managing Director, Bay City Capital

KARL HANDELSMAN
Founder, Codon Capital

DENNIS PURCELL
Founder and Senior Advisor, Aisling Capital

ISAI PEIMER
Managing Director, MedImmune Ventures

GREG BROWN
Founding Managing Director, Healthcare Royalty Partners



JOHN CHAMBERS
Vice Chairman and Head of the Healthcare Investment Banking Group, ROTH Capital Partners

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the market. Investors also held off buying on the dips, waiting for more momentum to build. In late August through September, almost two-thirds of bio IPOs were priced below the range, and almost two-thirds declined in value. Most companies were able to raise money during recent years because the market was so good. Now, the early-stage, proof-of-concept model is becoming even more important because Big Pharma is tending to make deals and acquisitions sooner rather than later.

Factoring in the Big Pharma viewpoint, a corporate venture capitalist shares some useful points on how to prepare for the investment climate in the new year — Isai Peimer of MedImmune Ventures:

> *It helps to deconstruct the situation and recognize how early-stage biotech investing is different from later-stage biotech investing in the types of investors. Close to $8 billion annualized investment goes into the biotech sector, around double the normal fund rate, and a lot of it is generalist investors in IPOs as well as mezzanine and even earlier-stage rounds. It is important to recognize the source of capital, because that determines how "sticky" it is.*
>
> *In late-stage investing, there are very legitimate reasons why the sector has attracted capital. Of course, investment flew out of declining sectors like energy, so it had to go somewhere, and luckily, biotech has experienced some constructive forces. The novelty and quality of science has greatly improved, and many new approaches are panning out with clinical data and new drugs on the market that provide a step-function benefit in treatment and care. The FDA has become a lot more constructive with its new regulations expanding accelerated approvals in our sector. For the past five years, we have had a steady stream of great companies appropriately going public and understandably creating great returns for investors.*
>
> *But if we continue to kind of go through turbulence, that will be painful. I worry about companies that have accepted money from investors who were counting on a constructive IPO market and may not have the time horizon flexibility to stick it out to the end. The fundamentals are still good, but I also recognize that there's been such an overrepresentation of generalist money, and I wonder where the generalist money will go. It will not go into the energy sector, not for a while.*
>
> *On the early-stage side, I don't believe much has actually changed. It's the same 100 or so companies being started every year. It's the same sources of capital, the same couple of dozen or so funds that do most of the early-stage investing. That hasn't changed.*

Greg Brown of Healthcare Royalty Partners outlines several factors that will likely make life science investment "flatter and more volatile" in 2016:

> *Capital markets tend to be cyclical, creating discontinuity in access to capital. The new year will be interesting for three reasons. Number one is the presidential election, and we've already seen that drug pricing will be a very attractive and compelling political football, so that will increase volatility in our sector.*
>
> *Reason two: When the Feds eventually raise rates, it will probably draw people out of the equity markets and back into fixed-income capital, which always has an impact. The nadir in both the Dow and the BTK (Amex Biotechnology Index) was on Feb. 1, 2009. The Dow is up 143 percent above what it was then, but the BTK is up 615 percent. So that was great — the Dow delivered a 2.5-times return, but the BTK delivered more than a 6-times return. That's pretty cool.*
>
> *But it also leads to the third reason for a less-stellar market in 2016. When the generalist money flowed out, the BTK dropped off of its peak of 4,262 in July and was down just shy of 4,000 in mid-October. So it will not be a great funding environment, particularly in the equity capital markets. Of course, VCs had unparalleled exit opportunities during the past few years in the IPO markets and M&A activity. Now they will likely be more cautious about the valuations — because they can be. But it still will be an environment where good science can be funded and good technologies can get capital.*

Another New-York based veteran, John Chambers of ROTH Capital Partners, steps back to take in a larger perspective on bio investment in the new year:

> *There has been a marked change in the nature of how investors looked at biotech during the past 15 years. We now have real earnings-driven, metrics-focused companies at the top of the pyramid — Celgene, Gilead, Biogen — that we can value and trade at a market multiple, which is quite attractive based on their growth profile. There are more than 500 publically traded companies in this sector. Before the past several years, there were approximately 300*

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companies at any given time, as M&A volume tended to offset the number of IPOs over this period. If the capital markets are functioning well, there will be fundamental investor interest. The market returned about 35 to 45 percent a year for the past four years, mainly because the larger players performed exceedingly well on their true metrics. When investors wanted to add value and punch to their portfolios, they would take the liquidity risk and go downstream to smaller cap names and hopefully, on a milestone-driven basis, get a higher return.

Many of the companies that have gone public haven't done a subsequent follow-on offering, so there is a large amount of pent-up supply on the issuer side. Yet funding tends to become more difficult late in the year; investors take on a risk-averse posture, especially with vagaries such as the current pricing debate. Going into 2016, companies will obviously look to the new issuance market again, but the fund managers will be much more discriminating. It's not going to be an exercise in getting a little capital to a lot of names. It is now more Darwinian – fund managers will say, "We've gone from roughly 300 companies to more than 500 companies; how many of them are delivering at a level where we want to continue funding them?"

Karl Handelsman of the startup-focused Bay Area firm, Codon Capital, foresees a continuing demand for novel bio assets in 2016, though with a higher bar of therapeutic impact and proof-of-concept.

> *If and when the boom times do end, there will be an even stronger need for a stable of very strong, especially early-stage projects that deserve to be moved forward into the clinic, as in cancer immunotherapy. The enthusiasm for cancer immunotherapy is driven by its ability to modify the course of a disease in an incredibly dramatic way. That experience was formerly limited mostly to people involved in treatments for rare diseases, where there is often a clear mechanism of action and where you can have some dramatic impact or it wouldn't be a rare disease. Cancer immunotherapy has caused so much excitement because people realize it is a game-changer, and it's a principle that can be exploited in many kinds of cancer.*
>
> *There is always a high-risk profile at the preclinical stage for novel approaches, and people always talk about clinical proof-of-concept in go/no-go decisions. But I think much more about whether an approach has a higher probability of success relative to others at this stage – and if it does work, does it really modify the disease in a head-turning, "Oh wow, this is fantastic" way?*

How can companies and investors manage the risk of drug discovery and development in the more "Darwinian" climate of the coming year?

Dennis Purcell puts risk-management into the context of the 2016 investment climate:

> *In the past, when generalist investors withdrew, it really created problems for the life science sector, but this time I don't believe it will, because the sector has matured. In relation to risk, a lot of money is now being poured into the venture capital world, so our job is to take on more risk. With the continued risk-taking by the VCs, the foundations looking for good early-stage technologies, the health systems entering the equation, and Big Pharma making deals earlier and earlier, we will continue to see a good level of investment at an early stage.*

Isai Peimer advises caution toward some new early-stage technologies but greater optimism toward the resurgence of others:

> *There are some therapeutic areas, such as immuno-oncology and gene therapy, where there's a broad conviction, maybe ahead of convincing data in the clinic. In those cases, a fantastic amount of investing occurs for anything and everything in the tool box, which is worrisome. That said, there is now a lot of good data for specific approaches. In gene therapy, recent trials show it is a great tool for monogenetic diseases, perhaps even transformative, with the potential of being curative. We invested in a company that entered gene therapy 10 years ago, when it was very unpopular. We IPO'd the company about a year ago, but we refocused it from diseases that were probably unsuitable for the technology into other areas, such as ophthalmic disease, where it is working out.*

Karl Handelsman sees new promise at the preclinical stage for earlier proof-of-concept and target validation:

> *It is perennially true what really matters is what we see in the clinic, but the animal models are getting better – more predictive of how to use a small molecule, protein, or antibody in the clinic, how it could fit into the standard of care, and whether a strong signal will emerge early in the clinic, validating the drug's mechanism of action and ability to modify the disease. We are quickly accumulating better tools and*

data to make preclinical models more predictive. CRISPR is a tool that will greatly accelerate discovery of different pathways and ways to fight diseases. We now also have a pool of talented professionals who have moved drugs forward into and through the clinic.

John Chambers recommends companies make the most of the remaining momentum in the public market:

> *Four IPOs were done within a month and a half after the pricing and reimbursement issue arose. Yes, they were done at a 20 to 30 percent discount to the midpoint of filings, but they indicate an IPO market still exists. They largely traded up, so there is a positive after-market, and maybe a few more will get done this year. There are investors looking for risk-mitigated companies, something that won't hurt them before the end of the year. If your company delivers on clinical data between now and the end of the year and wants to access the capital markets — even though your stock price might not reflect its de-risked value, it's your ticket to enter the market and gain access to the capital. You have a ticket to ride!*

Carl Goldfischer emphasizes creative, early-stage funding:

> *One of the benefits of having a really flush capital market cycle for bio is giving companies more leeway in funding earlier-stage, riskier assets. There is now a host of alternative financing structures being contemplated for early-stage assets, from the little companies that partner with a pharmaceutical company at startup, to universities that, with reduced NIH funding, want to be more creative about how they partner with VCs and pharmaceutical companies. A whole myriad of new structures and financings are arising at all of the major medical centers in cooperation with the market participants.*

Greg Brown sees more alternative funding models emerging:

> *Companies have become more adept at finding additional ways to fund new technologies. That puts a lot more focus on critical milestones, proof-of-concept, and being more careful with capital — a pattern I would expect to increase, not decrease, during the next year or so. That means more credit products, royalty financings, grant funding, and other nondilutive, nontraditional forms of capital. The need for capital is so inelastic, but access to capital is sporadic, and that's a bad combination. When the equity markets grow more parsimonious, we can enjoy more opportunities in the alternative-funding markets.*

What other issues, events, or trends could affect the life science funding/investment environment significantly in 2016?

A quick wrap-up initiated by Dennis Purcell:

> *Compared to most industries, the pricing and reimbursement issue will be a steady drumbeat. I don't think the election in 2016 will particularly change things, but the payers such as Express Scripts and United Health are being much more difficult, and we will be paying much more attention to them. Express Scripts writes a billion prescriptions a year and covers 85 million people. It will have a huge impact on our sector going forward. About 40 nonprofit health systems now have their own VC funds, so we will see more of the hospital systems act as the payer on the one hand, the provider of healthcare on the other hand, and an investor in these companies on yet another hand.*

John Chambers:

> *Companies should reach out to advocacy groups early on. There will be points when the groups are supportive, and other points when they look at pricing, and hopefully it will not lead to confrontation. But if you have these relationships, the advocates can educate you about the patients' treatment experience and help you come to a rational, but return-oriented pricing. Beyond the enormous cost of developing a new drug, companies have to be able to price within that IP-protected window to get a return; otherwise shareholders won't let the capital flow into the sector to pay for the innovation. The logic is a little circular, but when people realize what the R&D they and their insurers pay for accomplishes, they are much less likely to challenge every high price. Still, it is preferable that companies take guidance from the patients' expectations, rather than merely announcing a price and effectively saying "Take it or leave it."*

The other experts echo the thoughts in this "anything to add?" section, and the group as a whole offers more thoughts and experiences than we have space to share here. But rest assured — none of it will go to waste. Look for additional material from our exchange in our online "cutting-room floor" section and future editorial features in *Life Science Leader*.

Are Your Leaders Failing To Capitalize On The Power Of Social Media?

WENDY MANTEL

Ian Read, chairman of the board and CEO of Pfizer, has a personal LinkedIn page. However, his enviable status as a LinkedIn *influencer*, a label bestowed on an elite cadre of professionals, didn't come about just because of his complete and searchable profile, but because he is an active participant.

For example, Read has published on LinkedIn's PULSE nine times in the last 18 months. His career tips article alone has been read more than ***47,000 times***. The Pfizer CEO comes across as social media-savvy, articulate, sophisticated, personable, and reflective, and by extension, his polished image enhances the Pfizer corporate brand.

OUT OF SIGHT, OUT OF THE CONVERSATION

The most popular LinkedIn profiles in any company should be those of its C-level executives, since these are the people featured in press releases, company news, and the media. LinkedIn and other social media provide a wide-reaching, inexpensive forum for executives to manage their persona and enhance their companies' images. Why then does biopharma, an industry desperate to enhance its public image, seem so sorely underrepresented in social media? At this writing, fewer than half of CEOs of the 10 biggest biopharmaceutical companies have LinkedIn profiles.

A 2014 BRANDfog global survey of CEOs using social media shows that ***not*** participating in social media is a big strategic risk. Conversations on social media channels don't stop just because top managers aren't looking. When an executive fails to speak up, other voices fill the void, empowering those much-less-qualified and vested to shape a company's brand and influence its reputation.

POWER OF THE BRAND AMPLIFIED

According to the same BRANDfog survey, three trends will shape modern business communications:

- SOCIAL CEOS WILL MAKE BETTER LEADERS.
- SOCIAL CEO ENGAGEMENT LEADS TO BRAND TRUST.
- SOCIAL MEDIA IS MODERN PR.

Here's how to turn social media to strategic advantage at your company.

8 STEPS TO ESTABLISHING A SOCIAL MEDIA PRESENCE

Digital marketing expert Mark Schaefer suggests these steps to build corporate and leadership social media presence:

1. Identify social media objectives and strategies.
2. Assess the company culture — it needs to support social media's value to the organization.
3. Establish a social media lead team to build a plan and the necessary infrastructure to support implementation. This may require representation from IT, HR, the legal department, top management, and others.
4. Publish a company social media policy stating in black-and-white what employees are and are not allowed to post online about the company, its leaders, its products, research, stock, and so forth, and actions taken on policy violation.
5. Identify sources of content (e.g., blogs, podcast, videos).
6. Define your audience and where you can find them.
7. Determine how to measure success, and demonstrate progress towards goals and ROI or to make course corrections.
8. Choose the right social media platforms.

Solid planning will set you on the right course to become a social media influencer — as a leader and as your company's top management. It's up to you to become part of the conversation. L

Wendy Mantel is a certified social media strategist and president of Mantel Coaching, Inc.

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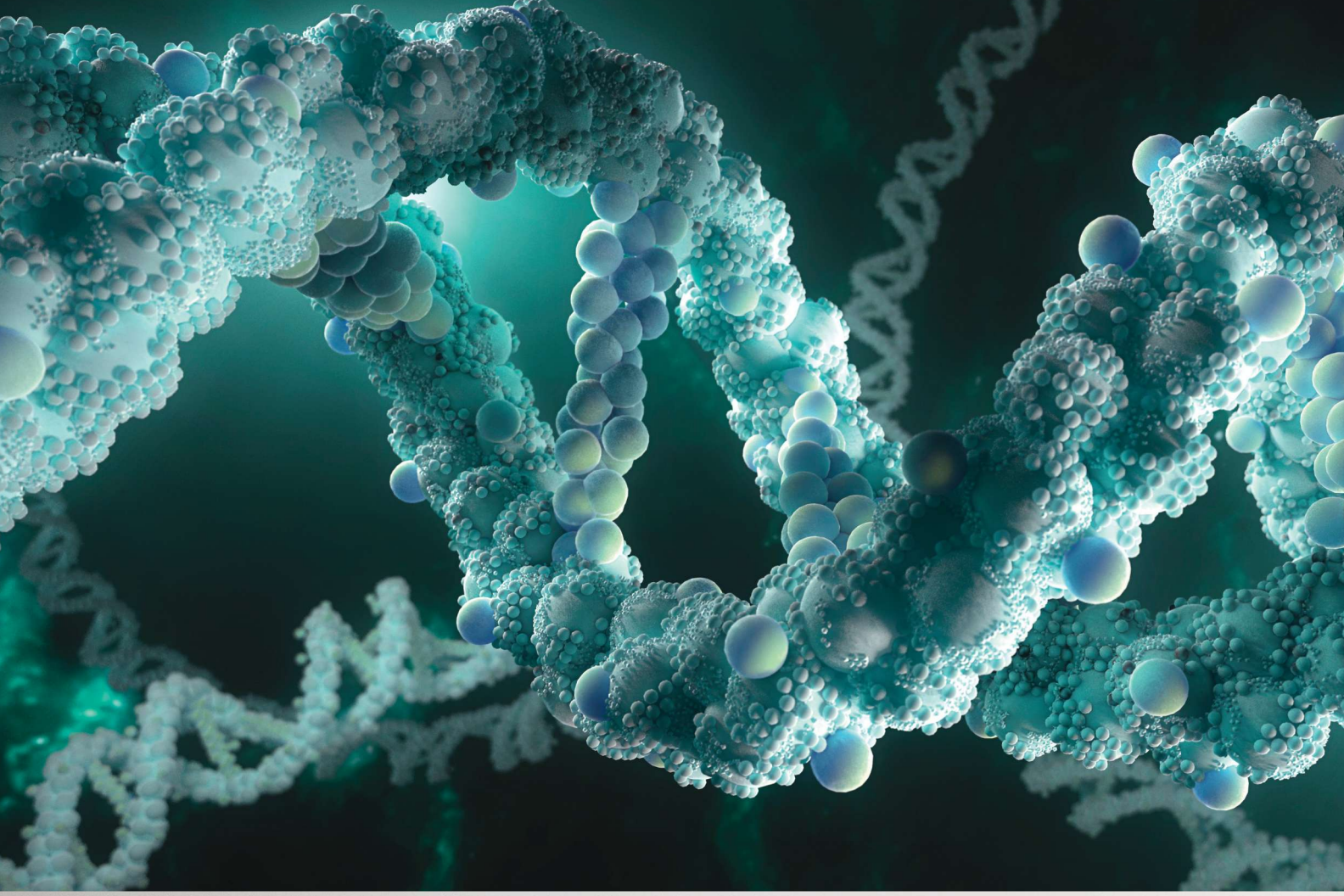

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