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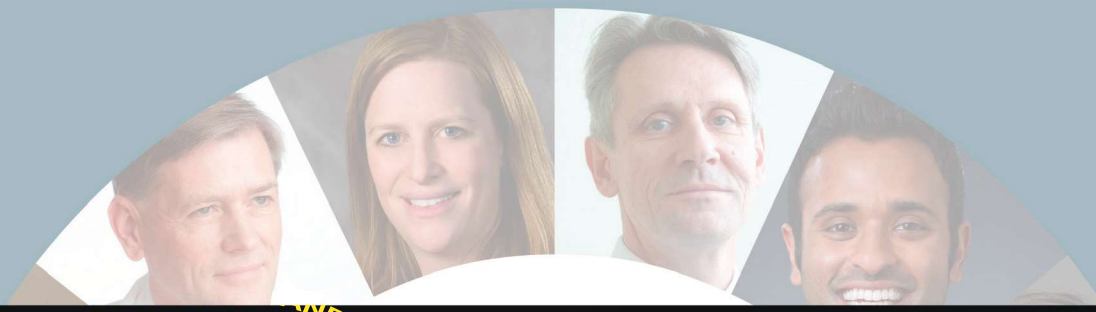

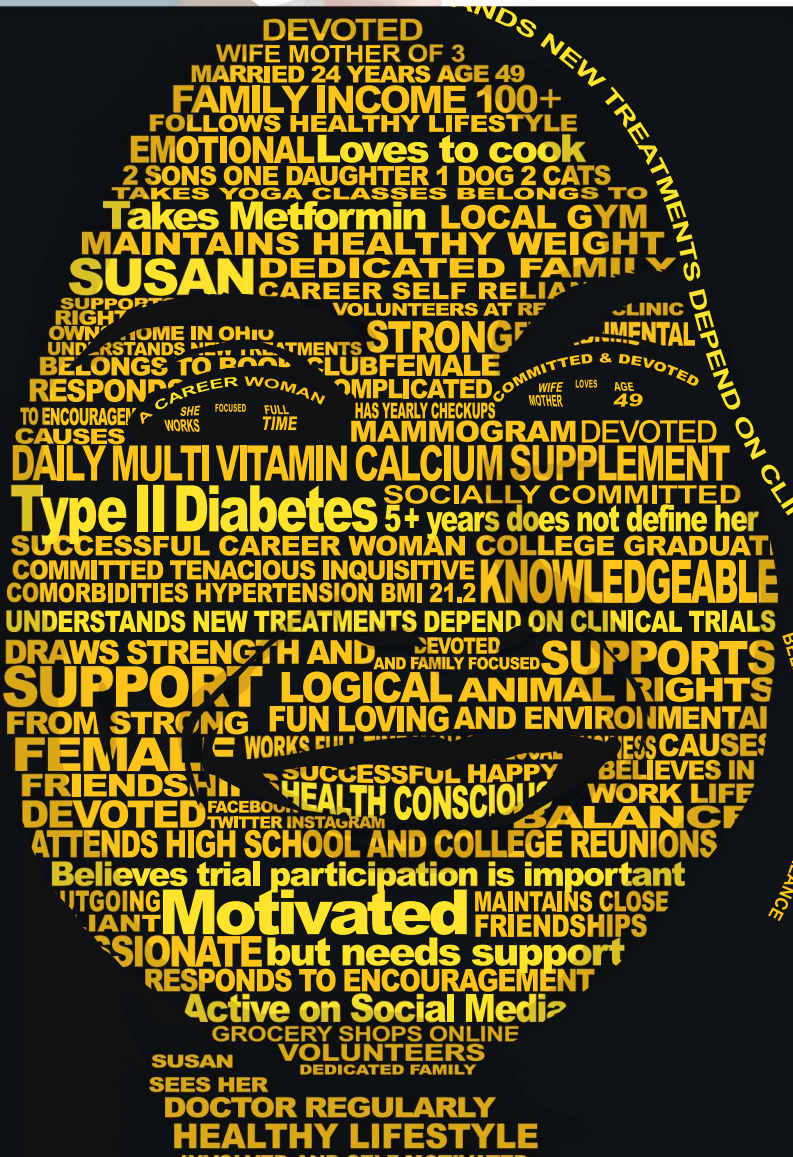

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And The Magic 8 Ball Says...

ROB WRIGHT Chief Editor

Remember the Magic 8 Ball, a fortune-telling device/toy developed in the 1950s? Manufactured by Mattel, the toy's "advice" is generated at random through a 20-sided die that floats inside a cylinder of blue liquid. Asking a question aloud, the person holding the Magic 8 Ball then turns it over, and the die surfaces to a window where its answer can be read. But could the Magic 8 Ball have predicted it would still be going strong today, or that it would be available as an online oracle and an official App on iTunes? "Reply hazy try again" is one of the 20 possible responses it might provide.

The art of prophecy (by supernatural means) is often referred to as soothsaying and carries a dubious reputation. While there are plenty of soothsayers who remarkably miss, there are others whose predictions are frighteningly accurate. For example, in 1964 Isaac Asimov ventured a guess at what you might find if you set foot inside the 2014 World's Fair. Now, despite the fact that a World's Fair did not happen that year, some of his forecasts were spot on:

- Kitchen units will be devised that will prepare "automeals," heating water and converting it to coffee.
- Much effort will be put into the designing of vehicles with "robot brains."
- Synchronous satellites, hovering in space, will make it possible for you to direct-dial any spot on earth.

You can find another fascinating example of accurate predictions in the movie *Steve Jobs*, which begins with a 1974 interview of Arthur C. Clarke (the science fiction writer behind *2001: A Space Odyssey*), who predicted by 2001:

- Every home will have a computer that is connected to the world.
- You'll be able to check your bank statements, make theater reservations, etc., and we will take it all for granted.
- Computers will enrich our society and let us conduct business from wherever we like, allowing us to live away from major cities.

The difference between soothsaying and the above examples are chance guessing versus *highly* educated deduction. At *Life Science Leader* we prefer to hedge our bets — steering toward the latter. That's why in this 2017 Outlook issue you will see some of the most well-known and highly regarded industry thought leaders and their forecasts. Inside you will find biopharmaceutical executives from Allergan, AstraZeneca, Bayer, Celgene, J&J, Novartis, Pfizer, Sanofi, Shire, and more. But we didn't stop there, because you only need to look at this year's U.S. presidential election to realize that even insiders can be surprised from time to time. For example, former CNN chief political correspondent Candy Crowley admits to having expected Donald Trump's campaign to have faded long before the Republican National Convention. So in addition to industry insiders, we also invited other highly regarded experts, such as a public policy, pharmacy, and economics professor; executives from health insurers, and so on. For if you want to get close to nailing a prognostication, ask yourself — is it better to ask those who are following the trends or a wide variety of those who set them. The number of thought leaders in this month's signature issue is unprecedented and the result of a lot of hard work by a very talented *Life Science Leader* editorial team. And while we hope you enjoy it, we trust we can count on your participation to make next year's issue even better. L

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Q What Trend Do You Expect To Be Big In 2017 – And Why?

A TRANSPARENCY IS THE NEW TREND. Our industry needs to make transparent how each end-user healthcare dollar spent gets shared between the innovator biopharma company, the insurance company, the pharmacy benefit manager (PBM), or the hospital or treatment center. If we don't make it happen, others will do it for us and create false perceptions (and there are plenty out there). Leaders from biopharma, insurance, PBMs, and providers will all need to sit at the table with congressional leadership and explain the healthcare reimbursement ecosystem. In congress, leaders will want and need to know who gets what for what. It is clear that innovators take enormous risk developing pipelines, and that cost is high. Despite people not wanting to hear about the cost of developing innovation, it does not mean we should stop explaining. Maybe courage is a new trend – the courage to stand up for transparency.

PAUL HASTINGS
is chairman and CEO of OncoMed. He has over 30 years of biopharmaceutical industry experience, which includes serving as chair of emerging companies section for BIO for over 10 years.

Q What Trend Do You Expect To Be Big In 2017 – And Why?

A THE POLITICAL DEBATES ABOUT DRUG PRICING will lead to an increased push for transparency across drug development and marketing. This will also create a lot of debate about exactly what transparency means. Patients and some legislators view this as a way to shame drugmakers into lowering prices so patients' out of pocket will be lower; by transparency they mean visibility into drug development costs and profitability. Biopharma companies feel insurance company practices unfairly focus patients' ire on drugs by making drugs more expensive to patients as compared to other medical interventions and services. Biopharma companies also feel the public and legislators don't understand how PBMs can also benefit from higher drug prices. Biopharma companies, therefore, want greater transparency around insurance and PBM practices. Transparency on its own will not solve the problem of out-of-pocket costs of drugs, but greater transparency would certainly better inform the public debate around real solutions.

RACHEL KING
is CEO of GlycoMimetics, a publically traded biotechnology company. She has nearly 30 years of experience in various management roles in the biotech and pharmaceutical industries.

Q What Trend Do You Expect To Be Big In 2017 – And Why?

A BUOYED BY A WAVE OF CHEAP MONEY from the banking system, urged on by short-term investors seeking returns, the biopharma industry has, since the Great Recession, experienced a wave of M&A and financial-engineering-driven deals such as corporate tax inversions that are often not focused on long-term innovation and real creation of sustainable value. Pricing excesses, especially prevalent in the so-called specialty pharmaceutical sector, are facing increasing curbs by regulation and negative media attention.

In 2017 you'll see more focus on investment in R&D, operations, and education of physicians and patients. CEOs and senior executives should be focused on volume rather than price growth. Increasing attention should be on differentiated science, on improving decision making on internal R&D programs, and on clinical-development excellence. In the final instance, CEOs should determine how much growth needs to stem from acquiring or licensing external R&D assets to drive successful long-term growth.

DAVID PYOTT
is former chairman and CEO of Allergan, and he serves on the boards of Avery Dennison, Alnylam, BioMarin, Royal Philip, and a Governor of London Business School.

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Washington Outlook For 2017: **Trump Takes The Helm**

JOHN McMANUS The McManus Group

Donald Trump's upset victory over Hillary Clinton upends Washington and the health agenda for the 115th Congress. Conventional wisdom held that a Clinton administration and a Democrat-led Senate would be focused on stabilizing Obamacare's healthcare exchanges and exploiting the growing public concern with pharmaceutical pricing with a raft of detrimental proposals and policies.

But the stunning Trump victory and the Republican hold in the Senate, giving the GOP full control over the executive and legislative branches (and delivering a major opportunity to reshape the judicial for the next generation), provides some breathing space for a pharmaceutical industry that increasingly felt under siege. The industry was bracing for an intensified wave of congressional investigations, efforts to price control elements of Medicare Part D, and Senators Bernie Sanders (I-VT) and Elizabeth Warren (D-MA) driving the FDA to be the utilization police via the must-pass Prescription Drug User Fee Act (PDUFA) reauthorization. Those immediate threats appear to have subsided when the "blue wall" of rust-belt states fell into the Trump column on election night.

The market reacted accordingly: biotech and large pharma stocks were up nearly 20 percent on the week. (Execs might have taken a more keen interest in Mr. Trump had they anticipated this reaction!)

Yet we now enter a healthcare policy environment lacking certainty. Candidate Trump's key health focus was to "repeal and replace" Obamacare. He provided little detail on what the replacement policy would look like. The campaign's website page on healthcare consisted of a skeletal outline of familiar Republican ideas:

- Allow insurers to sell coverage across state lines
- Provide tax deductibility of individually purchased insurance
- Improve and enhance health savings accounts
- Block grant Medicaid to the states.

But where would this leave the millions of people who had obtained coverage under the Affordable Care Act through Medicaid expansion and subsidized exchange plans? These exchanges are already in dire straits: dozens of plans have exited the market, and those remaining are substantially hiking premiums and deductibles. Moreover, reinsurance and risk corridor subsidies expire at the end of the year — the health insurance exchange will collapse without propping up.

Waking up to the complexity of our health marketplace and difficulty in repealing the ACA and wanting his focus and capital spent on tax policy or infrastructure programs, Trump is already walking back on some of his campaign pledges related to the ACA. Letting Congress deal with the issue might be wise relief, letting him serve as Trumpeter in Chief.

THE RYAN PLAN

Fortunately, House Speaker Paul Ryan (likely to remain in his role) has already dispatched his caucus to develop a blueprint of positions on critical issues, including repealing and replacing Obamacare. Ryan's "A Better Way" white paper outlines a comprehensive approach to replacing Obamacare as well as reforming Medicare.

Ryan's plan would replace the means-tested subsidies of the ACA with a flat, refundable tax credit available to all who do not have employer-sponsored coverage. It would repeal the benefit mandates of the ACA and leave the regulation of insurance to the states. It would replace the 40% excise tax on "Cadillac health plans" with a cap on the exclusion from health insurance for employer-sponsored healthcare. While key details are yet to be specified (e.g., the value of the tax credit and cap on the exclusion), it is a serious plan that could provide a real alternative to the failing exchanges.

Ryan's plan also leaves in place the $700 billion+ in Medicare and Medicaid cuts from the ACA (including the 50 percent hike on the prescription drug Medicaid rebate) and the enhancements to

Medicare Part D — notably the 50 percent-required manufacturer discount in the "donut hole" as well as improved benefit plan coverage. But the plan repeals all Obamacare taxes, including the annual pharmaceutical fee that totals more than $5 billion annually.

Congress is expected to tackle the repeal and replacement of Obamacare through a parliamentary procedure known as budget reconciliation. While most legislation requires the support of 60 senators and therefore bipartisan cooperation to enact law, budget reconciliation permits Congress to pass legislation on a simple majority vote. However, the legislation must be limited to items that have a material fiscal impact (i.e., repealing subsidies, Medicaid expansion, and taxes are germane, changing insurance mandates and advisory commissions are not). The 52-vote Republican majority makes this a feasible route, but empowers a single GOP senator (ahem … Ted Cruz) to wield enormous influence on the scope and details of such legislation.

After the election, Speaker Ryan signaled his intent to also advance conservative Medicare reforms outlined in "A Better Way," including raising the Medicare eligibility age to match Social Security and transforming Medicare to a competitive delivery system known as "Premium Support." That may be more than a President Trump is willing to swallow as his campaign said nary a word about entitlement reform.

But Republicans remain a party of small government and gravitate to policies that contain costs. That makes the recommendations from the June 2016 Medicare Payment Advisory Committee (MedPAC) of particular concern. It was the first time in the 10-year history of the program that the advisory council to Congress has examined the program and offered recommendations.

When viewed in their totality, they appear to be a PBM (pharmacy benefit manager) wish list for more control over who gets what, when, and how:

- Permit Part D plans to raise copays of brand-name drugs for low-income subsidy beneficiaries.
- Require physicians to provide more robust clinical evidence to appeal a formulary decision.
- Exclude the manufacturer 50 percent discount from applying toward the catastrophic threshold, thereby more than doubling the time the patient remains in the coverage gap.
- Eliminate two protected classes (antidepressants and immunosupressants).
- Empower plans to use more tools to manage specialty drugs.

While the Congressional Budget Office projects a flattening of prescription drug spending in Medicare through 2018 as a result of numerous patent expirations, costs are expected to more than double by 2026. However, Part D is projected to remain relatively constant as a share of Medicare spending — increasing from 14 percent of Medicare in 2016 to 15 percent in 2026. But there remains a dedicated alliance of PBM, health plan, and pseudoconsumer advocates fanning the flames on drug pricing and demanding legislative relief.

PDUFA REAUTHORIZATION

A paramount concern to the pharmaceutical industry will be the must-pass PDUFA reauthorization, which substantially funds the FDA with industry fees. The industry and FDA already reached an agreement on the measure. But that must now be enacted by Congress. While PDUFA was feared to carry potentially problematic riders in Democrat White House and Senate, it now may be an opportunity for more industry-friendly items.

But then again let's note that the general populist angst over pharmaceutical pricing may spur Congress, newly focused on the working-class issues coalition that elected them, to attach pricing and transparency amendments to the bill. A recent poll from the Kaiser Family Foundation found that 74 percent of Americans, including 68 percent of Republicans, feel that a top priority for government should be making sure medicines for chronic conditions such as Hepatitis C, mental illness, and cancer are affordable for those who need them.

Since President-Elect Trump is fundamentally unmoored by partisan ideology and has tapped into populist sentiment, it is not difficult to imagine his administration advocating such measures.

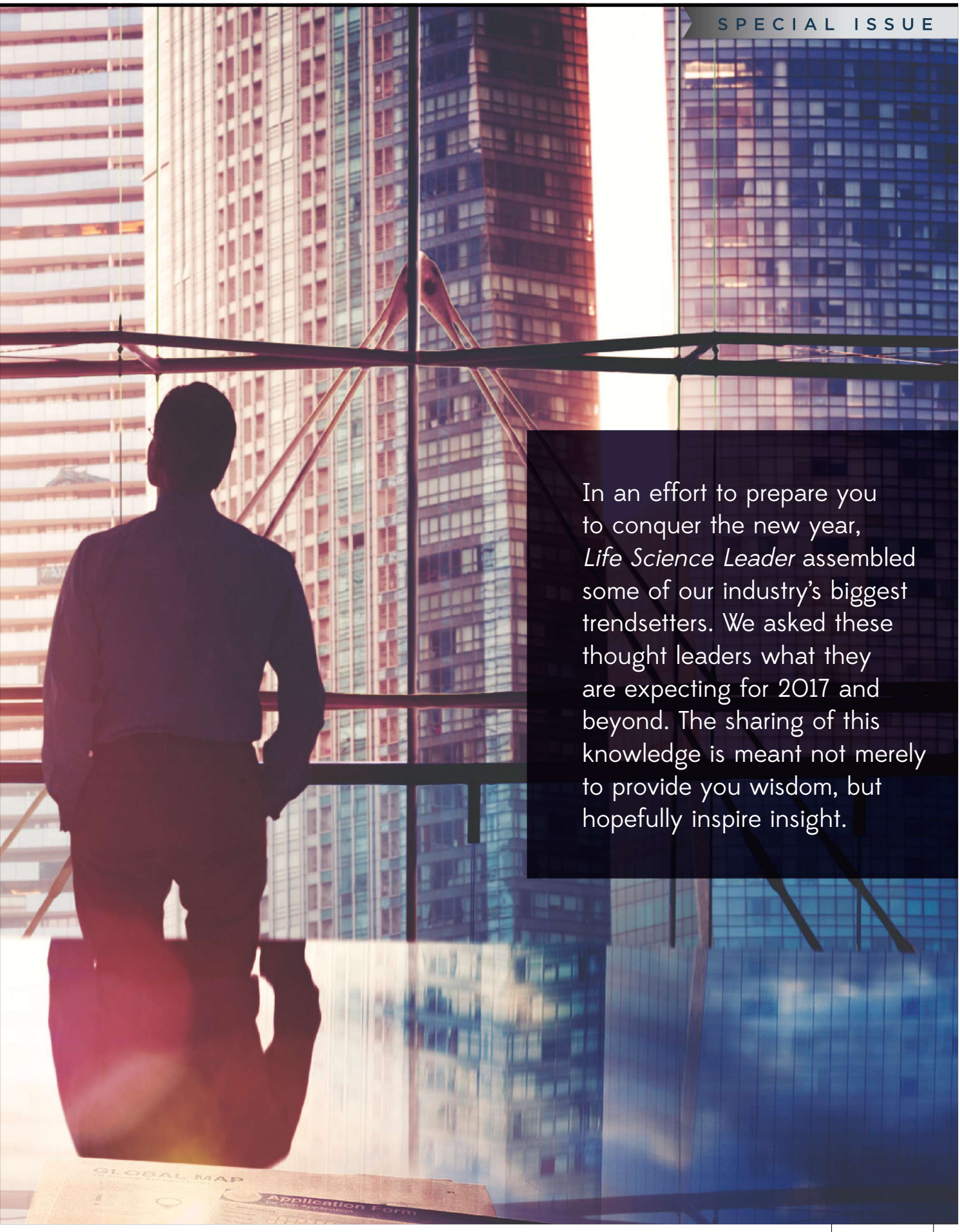
Republican control of Congress and the White House does not remove the spotlight from pharmaceutical costs and its impact on the budget and patients' ability to access their medicines. Rather, it calls for renewed engagement to educate policy makers on the cost-value proposition of pharmaceutical innovation and how it can constrain overall costs in the long-term. L

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

DON'T PANIC IN THE NEW YEAR, CONQUER IT

What 13 Life Science Trendsetters Expect For 2017 And Beyond

ROB WRIGHT Chief Editor @RFWrightLSL



In an effort to prepare you to conquer the new year, *Life Science Leader* assembled some of our industry's biggest trendsetters. We asked these thought leaders what they are expecting for 2017 and beyond. The sharing of this knowledge is meant not merely to provide you wisdom, but hopefully inspire insight.

WHAT U.S. TRENDS ARE GOING TO HAVE THE BIGGEST IMPACT ON BIOPHARMA IN 2017?

Flemming Ornskov, M.D., M.P.H.
CEO And Executive Committee Member, Shire

As an industry we need to do more to demonstrate the value of our medicines. One way we can do this is by appropriately leveraging technology. The ability of the biopharmaceutical industry to tap into the digital health revolution and forge effective collaborations with technology innovators for the benefit of patients will help determine our future success. Some ways in which technology partnerships will likely be useful include advanced therapies with specific disease targets, better diagnostics, "smart" devices for improved drug delivery, and disease management.

Mark Alles
CEO, Celgene

Concerns about access due to the cost of some newer therapies have created confusion and frustration, resulting in advocacy organizations challenging industry research efforts. Related to that issue is the trend toward improving understanding across stakeholder groups that patients with serious unmet medical needs are significantly benefiting from innovative therapies, thanks to the collaborative ecosystem between biopharmaceutical companies, payers, providers, government, and patient advocacy. Examples of collaborations include Vice President Biden's Cancer Moonshot Program, the 21st Century Cures Act, and the FDA's efforts to more rapidly approve innovative medicines and generic drugs. Biopharma will also be impacted by the demographic shift of aging populations in developed countries. Without medical breakthroughs to treat prevalent diseases of 50- to 70-year-olds, healthcare costs will continue to escalate.

John Maraganore, Ph.D.
CEO And Board Of Director Member, Alnylam Pharmaceuticals

We can expect continued debate on drug pricing in 2017 and beyond. Importantly, I believe the industry will work with policy makers to find a path forward that preserves the time-limited and market-based reward for innovation. Perhaps the solution will be greater industry support of more rapid FDA review of ANDAs (abbreviated new drug applications), leading to greater competition in the generic market. After all, our "social contract" is to accept obsolescence for drug exclusivity in return for a defined period where innovation is rewarded. Price increases, in the absence of additional evidence to support value, are hard to defend. Companies will need to learn how to grow through innovation, not arbitrary price increases.

WHAT GLOBAL MACRO TRENDS ARE GOING TO HAVE THE BIGGEST IMPACT ON BIOPHARMA IN 2017?

Christopher P. Austin, M.D.
Director, National Center For Advancing Translational Sciences (NCATS), NIH

Engaging patients as members of the research team at all stages of translational science (i.e., early-stage research to postmarketing) is providing important insight that can be instrumental in making the development, testing, and deployment of new interventions more effective. Another trend will be the emergence or re-emergence of epidemic infections such as Zika and Ebola for which new therapies and vaccines will need to be rapidly developed. While gene-editing technologies such as CRISPR-Cas9 will continue to improve and be increasingly applied in advancing science and disease treatment, they also present complex technical challenges, as well as safety and ethical concerns.

Jean-Jacques Bienaimé
CEO And Chairman, BioMarin

While the voice of the patient has always been critical in the development of therapies for rare diseases, it will become increasingly more influential in all types of drug development. Look for more collaboration between drug developers, patients, and regulators to identify clinical end points that are scientifically meaningful and demonstrate improvement in patient quality of life. Patients are also articulating their tolerance for risk from treatments, particularly for fatal diseases, and their expectations for clinical efficacy. This level of intersection between patients, drug developers, and regulatory authorities has the potential to bring about more and better treatments.

WHAT TRENDS SHOULD BIOPHARMA EXECUTIVES BE PAYING CLOSEST ATTENTION TO?

"The future in healthcare is about enabling whole-person care, not an individual pharmaceutical product. It's about integrating that product into the delivery of care to drive better, more affordable care. I've worked in pharma, retail drug distribution, and healthcare services and have seen up close the disconnects that can occur. A less-fragmented healthcare system will allow all of us to proactively help individuals better manage their health and lower total medical costs, not just pharmacy costs. Taking a broad perspective and creating thoughtful partnerships is the place to start."

Jeffrey Berkowitz *is EVP for the health-service company Optum. Prior to joining Optum, he spent six years at Walgreens overseeing the company's enterprisewide strategic relationships with payers, pharma companies, and wholesalers.*

Vas Narasimhan, M.D.
Global Head Of Drug Development And Chief Medical Officer, Novartis

Every year more than 36 million people are killed by chronic disease, a statistic projected to grow to over 70 percent by 2025. In addition to more people suffering from these diseases, chronic disease prevalence is increasing the economic burden of the already-rising healthcare costs around the world. Thus, I see the prevalence of chronic diseases as a major trend that will impact the biopharma industry as it strives to develop innovative treatments that improve standards of care.

WHAT TRENDS FROM OTHER INDUSTRIES WILL SPILL OVER INTO BIOPHARMA?

Alles: Big Data collection and analysis has transformed many other business sectors and is now a disruptive force in the healthcare and biopharmaceutical industries. The use of genomic and proteomic data with complex diseases (e.g., cancer) may allow for individualized treatment plans based on a patient's molecular profile, rather than the histologic origin of their disease. Big data is helping researchers better analyze patient information, correlate and understand the results from thousands of published clinical trials, produce real-world evidence, identify new molecular targets, and design better clinical trials. Big Data, by matching patients with the best available treatments, should not only improve outcomes, but also lower healthcare costs.

Austin: The application of advanced computing and Big Data approaches has entered biomedical research. As a result of recent scientific advances, there is a tremendous amount of biomedical research data, disease classification data, health records, clinical trials, and adverse event reports. These could be useful for understanding health and disease, as well as for developing and identifying treatments. Advanced data-sharing and computational approaches are needed to collectively mine this data to gain insights into the relationship between molecular and cellular processes and the signs and symptoms manifested in diseases. A trend from the movie industry that is occurring increasingly in translational research is that of collaboration to maximize effectiveness and minimize risk. We will see increasing partnerships among government, academia, industry, and nonprofit patient organizations.

Bienaimé: We are seeing more competition in the rare disease space for assets to in-license, and more companies are going after the same diseases with different and novel scientific platforms in disease areas with established treatments. In this highly competitive environment, which, by the way, is great news for patients with rare diseases, drug developers need to set the bar high on meaningful clinical outcomes. At BioMarin, we pursue drug development in molecules that are the first or the best in their class. We believe this creates a win-win situation for patients and the companies developing the treatments.

Stanley Crooke, M.D., Ph.D.
Founder, Chairman, CEO, Ionis Pharmaceuticals

The biopharmaceutical industry is clearly in the age of Big Data, beginning with genomics and other "omics" necessary for effective target selection. The ability to use the enormous amounts of information based on the natural history of human diseases, clinical trial

data, and postmarketing data demands even more effective informatics.

Ruud Dobber, Ph.D.
President AstraZeneca U.S.,
EVP AstraZeneca North America

Consumerism (i.e., patients driving their own care) is on the rise in healthcare. Technology advancements are allowing individuals to engage with their health in new ways and have the potential to improve quality of care, reduce costs, and increase the likelihood of patients reaching healthcare goals. While personalized medicine and services are the future of healthcare, success requires the industry moving from a fragmented way of engaging with patients to a coordinated experience similar to other customer-service industries. In an attempt to move in this direction, this year we launched AZHelps, a program that helps patients manage medication information, access savings offers, and access healthcare support through mobile devices and social media channels. We also have introduced Fit2Me, a free customizable cardiovascular and diabetes diet and lifestyle support program.

Maraganore: There appear to be many features of the film industry's evolution over the last couple of decades that could serve as a template for the future of biopharma. Specifically, the disaggregation from large studios into smaller groups (e.g., Universal Pictures to Focus Features, Fox Searchlight to 20th Century Fox). One could imagine how a similar trend could occur in biopharma between smaller biotechs, larger pharma, specialty pharmacies, and other distribution channels. Of course, the economics would need to be rebalanced, since the only way a biotech can build value for its shareholders is to directly commercialize its products, at least in the major markets.

Narasimhan: Machine learning and artificial intelligence are having an increasingly tangible impact on the biopharma industry, which I see as a huge opportunity. Data is the key to the next generation of care, which will center on true precision medicine through more individualized and targeted treatment. Emerging technologies that enhance our data analytics capabilities by enabling us to process data and learn more efficiently will help us innovate faster. Having a more robust understanding of diseases and individual patient needs has the potential to alter the way we conduct drug development. Our goal is to leverage data insights to one day outsmart disease.

Ornskov: There are nearly 7,000 recognized rare diseases, yet 95 percent of these lack a single FDA-approved treatment. On average, proper diagnosis can take nearly five years. This is because physicians frequently do not recognize the signs and symptoms, and patients and caregivers often lack information. As part of Shire's digital strategy, we are forming partnerships with rare disease online communities to help

WHAT TRENDS SHOULD BIOPHARMA EXECUTIVES BE PAYING CLOSEST ATTENTION TO?

"Obviously, the future of pharmaceutical spending is of primary salience. Countries around the world are increasingly relying on health technology assessment and other formulary tools – such as reference pricing and budget caps – to pressure innovators. Traditionally, the United States has avoided such tools, but they are making substantial inroads here. While product-specific evidence of value is important, there is a paucity of policy work demonstrating, at the industry level, value to society and reforms to guarantee access in an era of rising costs. Life science leaders need to develop innovative treatments, but that will not always be enough. They also need innovative pricing mechanisms that ensure the developers are rewarded when patients tangibly do better. Leaders also need to do a more credible job demonstrating the direct link between R&D today and health tomorrow."

Dana Goldman *is the Leonard D. Schaeffer Director's Chair and distinguished professor of public policy, pharmacy, and economics at the University of Southern California.*

WHAT TRENDS SHOULD BIOPHARMA EXECUTIVES BE PAYING CLOSEST ATTENTION TO?

"Drug Pricing Transparency: The discrepancy between public perception and industry reality regarding drug pricing reached a fever pitch this past election season, reinforcing the increased importance of transparency – a key biopharma trend. Fostering an open, honest, and objective dialogue regarding innovation, investment, and public health benefit is vital to combat the irrational vilification of the industry and points to the real culprits, such as rising insurance co-pays, PBM (pharmacy benefit manager) rebates, and other nonbiopharma factors. Industry executives, therefore, need to educate the public, media, and policy influencers regarding the truth behind drug pricing, societal value, and corporate accountability.

Off-Label Promotion: The surprising yet inexorable trend toward court-sanctioned off-label promotion is poised to transform how biopharmas communicate with healthcare professionals and potentially even patients and the public. The traditional ban on promoting drugs off label is being pitted against First Amendment rights, and the right to free speech appears to be winning out over FDA guidelines. Given the uncertainties and lack of formal guidance, however, biopharmaceutical companies should mitigate risk by closely following the court proceedings, remain current on the evolving FDA hearings and guidance, and strictly adhere to policy until advised otherwise.

Digitization of Commercialization: When it comes to bringing a drug to market, maximizing patent exclusivity has never been more important. Time is patent life, and more importantly, patient life, and the clock is ticking. Taking a molecule from a successful Phase 3 trial through NDA (new drug application) to commercial launch with speed and precision is critical to the long-term success of an in-market therapy, as well as to the patients whose lives depend on it. We have seen how biopharmas can struggle with transitioning from R&D into commercialized operations. However, some have begun successfully applying an array of digital technologies to evolve and execute faster in order to optimize their entire commercialization processes throughout the life cycle."

Leerom Segal *is a Canadian entrepreneur, humanitarian, philanthropist, and founding partner at Klick Health, one of the world's largest independent health agencies and biotechnology commercialization partners.*

those diagnosed to become part of an extensive network to track and improve outcomes. By connecting with, and learning from, others who've gone before them, patients with rare diseases have the opportunity to more proactively manage their conditions, while researchers can learn more about what is and is not working and try to develop better treatments to fill those gaps.

Michel Vounatsos
EVP And Chief Commercial Officer, Biogen

There is a lot we can learn from fast-moving consumer goods, particularly the way those companies contend with shorter life cycles and thinner margins and how doing so leads to their proactive management of resources. Consumer-focused companies also can teach us how to better engage with customers. While we work in an environment more regulated than most, we still need to get closer to patients and physicians and more effectively leverage digital and social media channels. For if we want to go beyond simply providing medicines, we need to engage in dialogue in the forums where these people increasingly turn.

HOW DO YOU THINK THE GLOBAL BIOPHARMACEUTICAL INDUSTRY MIGHT LOOK IN THE YEAR 2027?

Bienaimé: In a 2004 paper, geneticists Craig Venter and Daniel Cohen said that if the 20th century was the century of physics, the 21st will be the century of

WHAT TRENDS SHOULD BIOPHARMA EXECUTIVES BE PAYING CLOSEST ATTENTION TO?

"Payers are looking more aggressively at strategies that reduce their drug spend. These efforts often involve restricting access to various therapeutic agents by creating prior authorization or other requirements, generally in accordance with clinical evidence as well as the cost/value of the drug. But payers are also employing other tactics such as offering more narrow formularies that are sold at a lower premium and offer a lesser choice of drugs than the base product. The past year also has seen a rise in interest in outcomes-based pharmaceutical agreements that more closely align payment and value to the patient. This approach, while it may be unfamiliar to pharmaceutical companies, is one that has been widely employed in agreements with provider systems; therefore expanding and modifying the framework to include drugs seems a natural evolution.

By aligning payment and value, these agreements not only send a strong message to those who question the missions of both pharmaceutical companies and health plans but also are considerations in the prescribing decisions of the many physicians and providers who themselves have entered into payment frameworks that reward quality outcomes versus volumes of encounters."

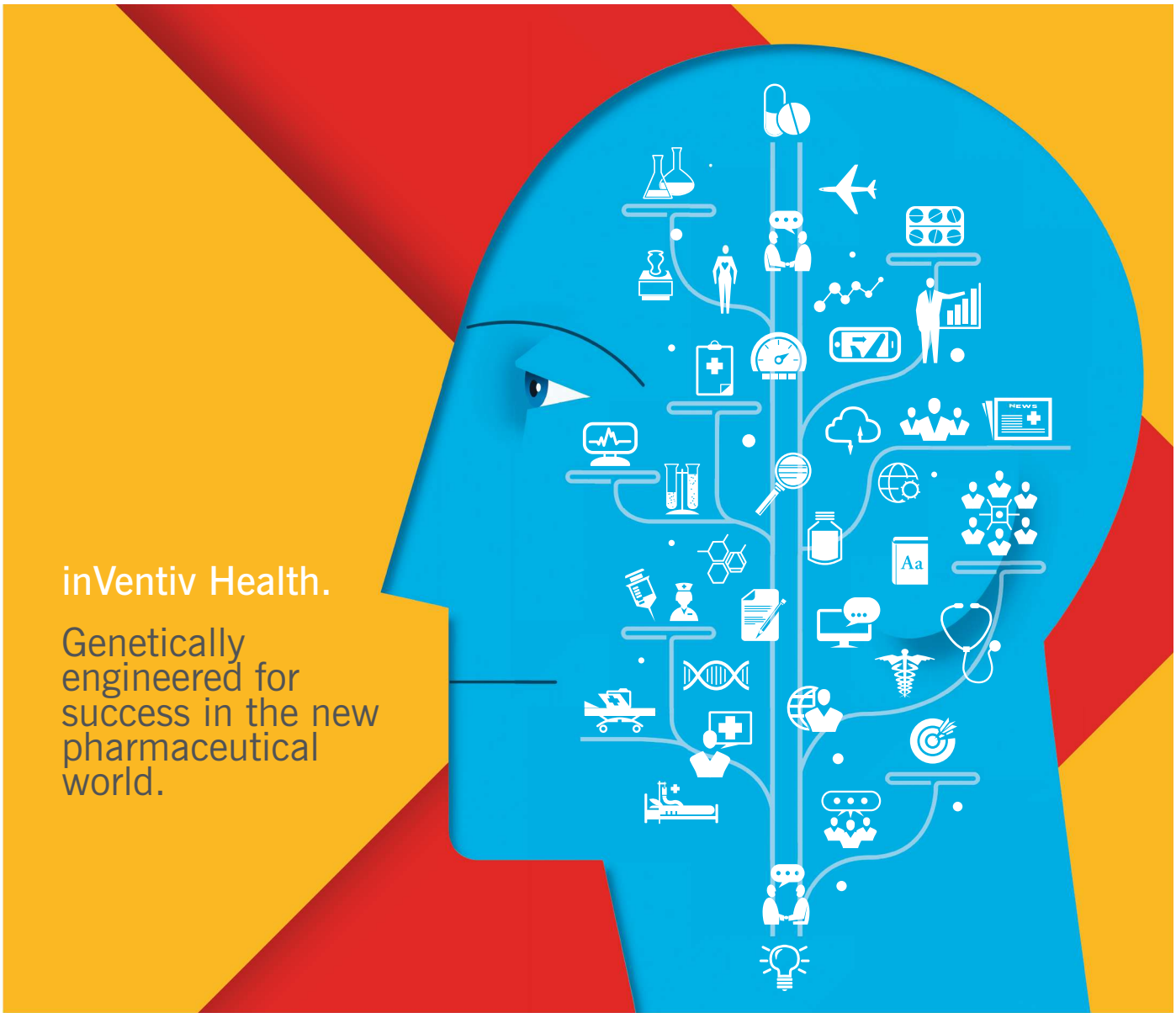
Michael Sherman, M.D., MBA, M.S., *is chief medical officer and senior VP for Harvard Pilgrim Health Care. He is also on the faculty of Harvard Medical School's Department of Population Medicine.*

biology. We are living that prediction. Never before has there been so much hope in our ability to cure diseases. Scientific discoveries have improved the outcomes of many diseases (e.g., targeted cancer therapies, antiretroviral therapy for HIV/AIDS, and a cure for hepatitis C). In rare disease, the sequencing of the human genome opens a whole new area to help identify and explore treatments for monogenetic diseases. As there is more clarity on the science of diagnosing the more than 7,000 rare diseases, we will see more companies developing treatments. The 21st century could have more personalized treatments, better diagnostics, more regenerative-medicine cures, and hope for global access to life-changing therapies.

Crooke: By 2027, industry and the drugs it produces will look quite different. Every major company will need to participate in all three major platforms for drug discovery: small molecules, monoclonal, and RNA-targeted therapeutics. Gene therapy may be validated for the modest numbers of diseases that are due to single-gene deficiencies. As pricing pressure increases, the traditional follow-the-leader strategy (e.g., develop the 4th PCSK9 inhibitor) will no longer be available. So companies that are successful will take greater target risk, be more generically innovative, and probably have a narrower disease focus than in the past.

Dobber: I began my career in the lab. Early on, I learned how important it is to push the boundaries of science and look for answers, even when things seemed unexplainable. I think the next decade will be transformational in terms of the medical advancements we achieve. The opportunities we are uncovering using personalized approaches or with immunotherapy are remarkable. We are coming to a turning point in the way we think about treating disease. In the next 10 years, I want to see the industry raising the bar even higher on what science can do for patients and the word "cure" becoming a part of every diagnosis conversation — regardless of the medical condition.

Vounatsos: Over the next decade we will see therapeutic innovation across diseases of the central nervous system. But it won't be enough to create breakthrough medicines. Because expectations are higher, industry will need to collaborate with physicians, patients, regulators, payers, and other key stakeholders in new ways. Diseases such as Alzheimer's, ALS, and Parkinson's exact a devastating toll on society and our healthcare system, and addressing these challenges will take more than the introduction of effective medicines. L



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THORNY ISSUES

Company Leaders Tackle The New Year's Toughest Macro Challenges

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

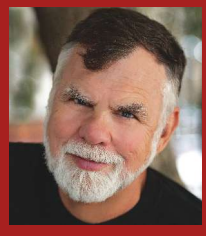
We posed some difficult questions to biopharma-company leaders on tough political, economic, and business challenges – those likely to become even tougher for the industry in 2017. The bravest among the invited answered our queries with thoughtful responses regarding thorny issues such as Brexit and the U.S. election, drug pricing and reimbursement, new life science business models, and the industry's technological future.

TO THE BRAVE...

Goes the credit for their thoughtful responses on some tough industry issues for 2017, as presented in this article. The following executives participated:

YUVAL COHEN
CEO, Corbus Pharmaceuticals

MARK GURNEY
Chairman And CEO, Tetra Discovery Partners



STEPHEN HURST
Founder, President, And CEO, Savant HWP

MARJANNE PRINS
Founder And CEO, OrgaNext Research

VIVEK RAMASWAMY
Founder And CEO, Roivant Sciences

KENTON STEWART
Senior VP, Health Systems Business Unit, Astellas

DIETER WEINAND
Member Of The Board Of Management Of Bayer AG, President Pharmaceuticals

Out of almost three dozen invitations sent to CEOs and business heads in biopharma companies of all sizes, we received seven responses. Aside from two executives from large companies, most of the respondents run small, entrepreneurial companies in the precommercial stages of drug development. Unfortunately, although more than half of the invitees were women, only one woman executive agreed to participate.

It may be useful to examine the most common reasons people gave for turning down the opportunity to participate in this forum. The most frequently used word, of course, was "busy" — providing input in the form of written answers to our questions would consume too much of the executive's time. The second most prevalent reason concerned the subject matter: Big issues are not the chief preoccupation for entrepreneurs.

Many executives apparently choose to ignore distractions such as the U.S. election and remain transfixed on the capital markets, perhaps assuming capital moves independently of politics, reimbursement pressures, business models, and technology. There is also an undeniable risk in commenting publicly on matters that seem beyond your control. Yet, as many people may be learning in the coming year, there is arguably much more risk in ignoring large-scale, extrapersonal issues. Our respondents also varied in how they managed the risk of commenting, either by the selection of questions each person chose to answer or by the degree of formality in their answers.

DONE IS DONE

As this is written, the national election in the United States still lies a week away, and our participants submitted all of their comments weeks earlier. Yet, though the election results will be known before our publication date, its actual effects will remain unknown well into next year. The executives willing to opine on the possible consequences took those conditions into account. All but one of the respondents answered the postelection question, and most saw both possible outcomes as negative, different only by degree — but to a great degree, at that. In short, most foresaw difficulty under Clinton but probable disaster under Trump.

Will the U.S. election affect your outlook for the life sciences industry in 2017? If so, to what degree and in what ways?

In a few words, **Mark Gurney of Tetra Discovery Partners** summed up the postelection scenario for the biopharma industry: "Drug pricing was a presidential election issue. Pricing will continue to be under pressure from the federal government."

Marjanne Prins of OrgaNext Research, based in the Netherlands, shared her European perspective on the presidential election in the world's leading super power. Prins expected Hillary Clinton would continue the work begun by the Obama administration with the ACA (Affordable Care Act) to vastly increase the number of U.S. citizens with health insurance, including needed reforms to the ACA legislation. Under Clinton, Prins also would expect private healthcare companies to start enforcing financial penalties for poor outcomes in line with the ACA. But if Clinton loses, the picture would be entirely different. "Trump is likely to turn back time and try to find a way to reverse the ACA and leave many millions uninsured," said Prins.

Victory by either party in Congress could have ill effects on the industry, according to **Stephen Hurst of Savant**: "I'm more concerned about the outcome of the Senate majority than the presidency. A Clinton presidency combined with a Democratic Senate majority would create additional uncertainty with regard to healthcare equities and make it more challenging to raise capital for life sciences companies in 2017," Hurst said. "It would also fuel the firestorm over drug pricing. Considering the poor job our industry leaders have done to date in responding to the issue, it certainly won't help our industry to face further public inquiries by Congress." Although a mixed victory with, say, Trump as president and a Democratic senate would mean a virtual status quo — in other words, stalemate, Hurst said. But the reverse could be destructive, he implied. "A Trump presidency with a Republican Senate could generate intense pressure to amend, if not abolish the Affordable Care Act, with the resulting uncertainty having a devastating effect on healthcare equity markets that could depress the entire stock market."

The response by **Vivek Ramaswamy of Roivant** adds some context to industry-related public debate accompanying the U.S. election. "This election has demonstrated that large segments of the American public are unhappy with the state of the union, and Pharma is not immune from that frustration." Ramaswamy cited a recent Kaiser Permanente poll in which only 56 percent of U.S. respondents said prescription drugs developed over the past 20 years had improved the lives of Americans, down from 73 percent eight years ago. In the same poll, the portion who said prescription drug prices are "unreasonable" climbed to 77 percent — 5 points higher since last year. "Election season is coming to an end, but public anxieties over the development and cost of prescription drugs are not going away anytime soon."

Because both major parties and candidates in this election have criticized drug prices, **Yuval Cohen of Corbus** also anticipated rising pressure from the pricing issue — but not uniformly industrywide. "Sectors exempt from this pressure will be novel drugs that offer clear benefit to patients as well as drugs for orphan diseases which serve very small, neglected populations with very high, unmet medical needs," he said.

Kenton Stewart of Astellas gave an even more opti-

mistic summary of the postelection landscape for the industry. "Every election provides a unique opportunity to have a forward-looking discussion on how we can make healthcare about individual patients and what is in their best interests," he said. "Regardless of party, there's broad agreement that we're living in a transformative period in which medical invention will help improve, extend, and save lives."

Stewart also made reference to a public-opinion poll, this one by the Galen Institute and Center Forward, which found nearly eight out of 10 voters want members of Congress to adopt public policies that help support new medical discoveries, and nearly two-thirds of voters hope the next president will make the issue a priority in their first 100 days. "In short, there's significant momentum for a propatient, pro-innovation, and nonpartisan agenda in 2017. Astellas is thrilled at the prospect of continuing to lead this timely conversation," he said.

BREXIT BREAKAGE

In the United Kingdom and Europe, an earthshaking vote already occurred last June, when the British chose to leave the European Union, a move popularly known as "Brexit," then awoke the next morning to consider all of the consequences. But the shock waves may have struck especially hard in the biopharma community, at least in the most immediate ways. Six of the seven respondents answered the following:

How do you see other macro events, such as Brexit, affecting the industry in 2017?

Bayer's Dieter Weinand placed his views on Brexit into a strong plea for measures to soften its negative effects on the industry's role in trade, research, and medical progress — most of all, in the nation now committed to life outside the EU. "The well-being of patients and the competitiveness of the United Kingdom could be at risk if we cannot find a way of ensuring the U.K. continues to benefit from EU policies and processes related to life sciences," said Weinand. "The EU and the United Kingdom must ensure that the British exit proceeds in a way that minimizes negative economic and social impact.

"This means that politicians will have to address complex questions, for example, related to the centralized European regulatory system. We see a strong need for harmonization and the continuity of EU regulations relevant for life sciences as well as common standards in terms of IP and patent requirements."

Weinand said regulatory harmonization is key to achieving sustainability of research funding for the life sciences, preventing potential delay in access to medicines for U.K. patients, and avoiding additional barriers resulting from tariffs and a reduction in free movement of people. "For the pharmaceutical industry, it will be important that all parties involved can find a compromise that does not undermine patient access to life-saving drugs nor threaten innovation."

Prins of OrgaNext envisioned a variety of possible effects of the British exit from the EU. "It will be interesting to see what will happen with the European Medicine Agency (EMA) and grants from the Horizon2020 program," she said. "It is to be expected to take a while before we see any concrete actions — but this insecurity will make British partners in science and business less attractive for long-term projects." Although the pound will likely deflate even more, Prins predicted, London will try to find ways to remain a major stakeholder in the financial markets, probably offering some innovative tax incentives. "But I would expect multinationals to set up shop in other EU countries, as access to money and talent in Great Britain declines in the future. Amongst my children's peers, there has already been a shift in selection of universities for their Masters' and Ph.D. programs. The U.K. is no longer high on their lists."

"It will take some time for the U.K. and the EU to sort things out, so I don't see much changing in 2017. Now if other countries in the EU follow in the U.K.'s footsteps in 2017, global financial markets will face uncertainty that will hurt our industry," said **Hurst** of Savant. Hurst voiced more worries about the Chinese government's monetary policy, expecting negative effects if China continues to restrict the flow of capital out of the country. He also expects negative consequences from the contraction of foreign healthcare spending by China early in 2017. "It's difficult to predict the magnitude of the impact, but I for one will be looking at China more than Europe with a watchful eye in 2017."

Cohen of Corbus, dissenting from the previous views expressed by respondents, took the perspective of the "let's not sweat Brexit" school. "While there is some concern regarding the EMA, which is based in London, I'm doubtful that such an event will have implications for the industry in the upcoming year," he said. "If there are indeed any ramifications, it is unlikely that we will see the effects beyond the U.K."

Tetra's **Gurney** also expected most of the ill effects of the EU exit to fall on Britain itself: "Brexit may slow down partnering by U.K.-based pharma companies such as GSK. Brexit may also slow U.K. biotech growth as access to EU funding mechanisms ends."

But **Ramaswamy** of Roivant believed the repercussions would spread more widely over time. In the short term, he foresaw few changes until the country invokes Article 50 to formally leave the union — a rupture delayed by a court ruling requiring Parliament to oversee the exit. "The EMA is still housed in Canary Wharf for the time being, and the U.K. will almost certainly adopt ICH (International Council for Harmonisation) guidelines when it leaves," said Ramaswamy. "But Britain's departure from the EU will eventually result in increased regulatory complexity, and European collaboration on R&D will be hampered in various ways, both large and small. More broadly, nationalism and protectionism are

growing forces on both sides of the Atlantic that could do real damage to scientific collaboration, the pace of medical innovation, and the adoption of improved therapies."

PUBLIC POWER, PRIVATE PRESSURE

Industry advocates traditionally emphasize government interference as the greatest threat to biopharma business and innovation. But many of the measures that have proved most challenging to the industry have arisen from other healthcare business sectors, including restrictive drug formularies, therapeutic substitution, "cost-sharing" co-pays and deductibles, and other ways of limiting patient access to higher-cost medicines. Asked directly, our respondents reflected the reality on the ground.

Will private payers – healthcare insurers, managers, and PBMs (pharmacy benefit managers) – or government present the greatest challenges for pharma, biopharma, and other life sciences companies in the coming year?

Ramaswamy of Roivant refused to put the blame on either set of external players — government or payers — for challenging the biopharma model, saying the "greatest challenges for pharma, biopharma, and other life sciences companies" are internal, not external. "They include complacency and path-dependent stagnation in R&D innovation," he said. "Instead of blaming regulatory agencies and private payers, it would be far more productive for our industry to turn our gaze inward and focus attention on improving efficiency in the process of delivering innovation. Viewing private payers and government as opponents, rather than customers and stakeholders, betrays a lack of understanding. Pharmaceutical companies, insurers, and government each want to do a better job of delivering superior healthcare to patients. This is our greatest common challenge, not one another."

At the other end of the size-and-complexity spectrum, Bayer's **Weinand** echoed the previous sentiments in advocating close collaboration by all stakeholders in the healthcare system to ensure continued patient access to innovative medicines. Yet Weinand acknowledged competition to secure funding for "new treatments with significant value for patients" will only intensify as healthcare budgets continue to come under strain, even as he expressed confidence in innovative medicines as solutions for those budgetary challenges.

"In the United States, various players such as healthcare plans or PBMs will likely further develop approaches for volume management [like step edits and prior authorizations], selective pricing pressure through formulary listing decisions, and deal-making for specific topics," Weinand said. "Innovative medicines help put healthcare systems on a sustainable path and ensure medical progress for patients in need. But altogether the market is highly competitive and it is likely that the competitive intensity will increase over the next couple of years."

Savant's **Hurst** was less sanguine. His view of the climate for biopharma in the larger healthcare environment portended some stormy weather. "The greatest challenges will come from patients in 2017, as we're seeing now," Hurst said. "I cannot predict who among the payers will pick up the charge once we're out of the election cycle, but unless our industry leaders start addressing patient concerns effectively, 2017 is going to be a tumultuous year for the industry. The current focus is on drug pricing, but devices, diagnostics, healthcare delivery, and the enormous disparity in hospital-services pricing are all likely targets."

Prins of OrgaNext predicts private payers will present the biggest hurdles for the industry in 2017 — if only because any legislation resulting from political speeches will develop slowly. But Prins warned of more long-term pressure on the legislative front. "As power shifts to payers and people, the marketing dominance of Big Pharma is becoming less and less, while the pressure to legislate more will become stronger. I anticipate continuous loss of jobs and M&A activities. At the same time this provides an opportunity for small companies to make a difference. But this is also due to the changing demographics, as well as the outrageous pricing and shifting power plays of some pharma companies. In the Netherlands, this has resulted in legislation being prepared to financially penalize out-of-stock situations that create interruptions in the supply of vital medicines."

Emphasizing a brighter alternative, Astellas' **Stewart** called for a future where cooperation ultimately reigns among the now contentious healthcare sectors. "This highlights a clear opportunity in healthcare that no one sector has successfully achieved (at least during my career)," he said. "We have to come together as a team and fully grasp the need to refocus the healthcare conversation on what is best for individual patients, for our economy, and for the health and well-being of our nation. Above all, everyone in healthcare benefits by preventing, managing, and curing disease. In this regard, I'm hopeful that 2017 will be a turning point."

Cohen of Corbus seemed to take a middle position. "The pricing debate will present a significant but not an insurmountable challenge, mainly given that there are multiple actors with competing interests," he said, adding a thought that somewhat anticipates our next question. "My prediction is that a compromise will be reached which will be acceptable to every party, probably in the form of further transparency on pricing/rebates and maybe even granting Medicare the ability to negotiate pricing for certain drugs. It's the Specialty Pharma sector that I think will take the biggest hit. I expect orphan drugs to be unaffected by this debate."

COMMON GROUND OR HARDER STANDS

Only five of the seven respondents chose to answer the following question. This may be one of the toughest of the "tough issues" we wanted to explore here, and to some extent the answer is already clear. Since our roundtable on drug pricing published in our July 2016 issue, the respective parties in the pricing debate have only reinforced their positions — in the case of industry association PhRMA, officially, and in the case of large payer groups such as Aetna and ExpressScripts, in more stringent restrictions on access to high-priced medicines.

Will pharma companies, payers, patients, and other stakeholders move toward a mutually satisfactory resolution of the drug-pricing controversy or take even harder positions on the issue in opposition to each other?

Gurney of Tetra sounded hopeful: "There has been movement toward the middle, with companies announcing voluntary price reductions, or in the case of the Mylan EpiPen, offering a generic version at a reduced cost."

But Roivant's **Ramaswamy** struck a more pessimistic, and perhaps realistic, chord. "In our polarized political culture, intransigence is more likely than reconciliation. While patients often fail to appreciate the tremendous risk and expense of drug development, it is also true that too many established pharmaceutical companies rely on price increases rather than thinking creatively about how to minimize the cost and time associated with bringing valuable new drugs to market. Instead of tired slogans, we need innovative solutions that bring down costs without sacrificing quality — and share the benefits of a more efficient R&D model with downstream stakeholders in the healthcare system (most importantly, patients). Until that happens, participants in this debate will continue to talk past one another."

OrgaNext's **Prins** put similar thoughts even more succinctly: "In the foreseeable future I am sorry to say that I expect more of the same; even harder positions would be my expectation."

"Our industry leaders need to step up and get in front of this issue, or it is going to get much worse," warned **Hurst** of Savant. "I have not seen or heard a single thing from anyone in our industry that is reassuring to stakeholders, and until that happens, we can only expect the nonbiopharmaceutical stakeholders to take even harder positions. Our highly compensated industry executives are not earning their money when it comes to this issue at this time."

But Corbus' **Cohen** voiced confidence in practical circumstances as a solution driver. "Regardless of their competing interests, none of these parties is interested in having a solution imposed on them by Congress," he said. "I expect a compromise will be reached that will be acceptable to all. They might not like it, but the alternative is much worse for everyone."

DEFENDING OBAMACARE

Prescription fulfillment has risen significantly in the United States under the ACA, yet PhRMA is taking a harder stance against "government interference" in pharmaceuticals and healthcare. Comment?

"It is understandable that the industry would like to have less government interference, but times have changed, and we better work with the new reality instead of clinging to the past," said **Prins** of OrgaNext. "Many markets have been revolutionized by new entries like Google, Amazon, Netflix, Uber, and Booking.com. It would be naïve to expect our market can continue in the ways of the past. To work with the other stakeholders is the only winning way forward, and business models need to change in order to do so successfully."

Savant's **Hurst** elaborated on his criticism of industry leaders. "PhRMA is not seeing the big picture and is in danger of becoming irrelevant," he said. "At last count, government is the largest source of revenue, and I believe that the days of 'pay and look away' are over. PhRMA needs to engage with the industry's biggest customer and educate them as to the complexity of our industry. Fundamentally, the industry is about ethics and the tension between autonomy, in this case free markets, and the obligation, especially in healthcare, to first do no harm. This tension is where we must live and where we must engage. In the case of prescription fulfillment, it would appear that government interference is a good thing. Perhaps we should admit that, take a lesson from it, and attempt to get the same outcome in other areas of attempted government interference."

Stewart of Astellas added these thoughts. "We welcome any and all ideas that will help improve our nation's healthcare system. We support patients' access to prescription medicines, which are essential to improving health and lowering costs. That is why we supported the enactment of the Medicare Prescription Drug Program [Part D]. The program, which provides affordable prescription drug coverage for more than 40 million seniors and persons with disabilities, has repeatedly come in under budget since it was implemented in 2006. Premiums have remained very low and patient satisfaction is high."

Stewart maintained the structure of the Medicare Part D benefit, in which private-sector negotiations between drug manufacturers and insurers keep costs low and provide seniors choices of plans, has been proven to work and serves as a guiding example for industry cooperation with government. "We must assess how to ensure and protect both sides when developing healthcare policy today. We'll continue to work hard to show what's pos-

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sible when our collective efforts are focused squarely on the patient."

"It is a mistake to present all governmental involvement as unnecessary interference," said **Ramaswamy** of Roivant. "In our present system, the federal government has a vital role to play in ensuring patient safety and access to care as well as funding basic research. PhRMA is right to push back against proposals that would stifle the development of new treatments, but not all change is negative. Instead of the status quo, what we need is better funding for the FDA so they have the requisite resources to clear the ANDA (abbreviated new drug application) backlog and promote greater competition among generics. Rather than simply reacting to alleged government overreach, the industry as a whole ought to be more proactive in supporting positive changes that help patients."

MODELING FOR FUTURE

The next question drew responses from five of the seven participants. Because specialty pharma has ballooned as a sector and also attracted most of the public criticism for "price-gouging," it is fair to ask whether it or any other business model will grow to dominate the industry.

What are the business models or model that will become (or remain) most prevalent or popular in the industry next year – e.g., specialty pharma, "traditional" (rDNA-based) biotech, orphan-drug, crowdsourced, and so on?

Tetra's **Gurney** gave the briefest response to the question, "All of the above," and Bayer's **Weinand** gave the most comprehensive one. "As an industry, we can create the greatest value for patients and all of our stakeholders through innovation. As such, I expect next year and for many years to come, the most prominent business models in the industry will be those that endeavor to discover and develop innovative therapies that address serious unmet medical need. At Bayer, we expect innovation that produces breakthrough therapies to be increasingly important in the competitive healthcare industry."

Yet Weinand also recognized an important role for incremental innovation such as specialty drugs that employ improved formulations or delivery. "Medical progress also happens in incremental steps, and these improvements can turn out to be game changers, finally transforming fatal diseases into more and more manageable chronic diseases," he said. "Additionally, companies need to demonstrate the value of their products to patients, providers, and payers through robust clinical data and real-life evidence in a way that effectively uses all relevant channels so they have credible information when and how they need it."

Weinand added an important element for the dominant model among large biopharma companies such as Bayer, now or in the foreseeable future— externalization of R&D. "Open innovation is a crucial element of pharmaceutical R&D and a key element of our innovation strategy at Bayer. With respect to the sources of innovation [e.g., "traditional" biotech, academic collaboration], I would not expect a dramatic change next year. Companies continue to collaborate with more traditional sources but also will continue to experiment with different approaches." He also endorsed the idea of crowdsourcing in research, citing examples in Bayer. "With our Grants4Targets program we have been an early adopter of crowdsourcing in drug discovery. Based on the success of this open innovation tool, we have expanded it by Grants4Apps, PartnerYourAntibodies, Grants4Indications, and even Grants4Traits [in CropSciences]."

Weinand's multiple-model description resonated with a more prescriptive treatment by Roivant's **Ramaswamy**, who eschewed the idea of a dominant model. "We will continue to see a proliferation of different approaches tailored to specific sectors of the industry," he said. "New business models in healthcare are already emerging that draw upon ideas from other industries: an emphasis on the 'long tail' of overlooked conditions instead of the usual suspects (Netflix), a turn to sharing resources and assets instead of outright ownership (Airbnb), vertical integration and optimization up and down the supply chain (Amazon) value investing (Berkshire Hathaway), and the like. Traditional one-size-fits-all pharmaceutical business models are a thing of the past. We will continue to see more innovation not only in the context of scientific advances, but also in the business models through which scientific innovation is delivered."

"I don't expect a revolutionary change in business models in 2017, but I anticipate more involvement of ordinary people in patient groups, crowdfunding, and advocacy for more access to care," said OrgaNext's **Prins**. "I also believe that the success of immunotherapy will attract different players to the arena, such as stem cell treatment labs for, amongst others, oncology and Alzheimer's.

Cohen of Corbus had a list of specific "models" or new trends among existing and emerging industry players: "I expect to see an acceleration of the shift from Big Pharma developing drugs in-house toward acquiring early and late-phase assets. I expect to see more and more personalized medicine and biomarker-driven developments such as CRISPR and CAR-T accelerate, although they will encounter pricing challenges. I expect to see an increasing proliferation of companies targeting orphan diseases which are lacking in treatment options and offer some clear pricing and IP benefits. I expect to see more and more patient advocacy groups, like the $4B Cystic Fibrosis Foundation, take a role in financing the development of drugs for their diseases."

MANIA FOR MERGER

Late this year, several Big Pharma deals, such as Pfizer's purchase of Medivation, raised speculation that merger mania may strike the industry once again in 2017. Three of our respondents commented on the situation.

To what extent will merger fever overtake the industry going into next year?

"I predict it will increase," said Corbus' **Cohen**. "Pipelines are in dire need of exciting new drugs and often late-stage ones at that. The only choice is to buy those at a premium through either M&A or licensing." Tetra's **Gurney** concurred. "Buyers for small to midsize companies are active in the marketplace. Look both to Pfizer and Allergan to pursue acquisitions of $1-10 billion companies to acquire products."

Ramaswamy of Roivant had a different view of the matter. "Fueled by low interest rates, expiring patents, declining productivity in R&D, and a need for new blockbuster drugs to maintain revenue growth, the frenzied pace of M&As has received top billing in the trade press. But in many ways, the more interesting story of the past few years has been the simultaneous increase in spinoffs of internal divisions — including divestitures of promising R&D-stage assets. Instead of a straightforward story of industry consolidation, what we are seeing is increased specialization in a hasty effort to come up with the 'next big thing.' As companies shed prior assets in order to focus their attention on that search, there will be tremendous opportunities for scientifically minded buyers who can sort the valuable from the dross."

WHERE TO BIOPHARMA?

Our last question here may seem wholly technical, but the answers — here best presented verbatim — reveal the strategic importance of this topic.

Is biopharma moving away from biotech – now, next year, beyond (more small molecules/peptides/bispecifics vs. rDNA proteins/fermentation)?

The response from Savant's **Hurst** forecasts a diverse technological and scientific future for what we now call the biopharma industry. "Small molecules tend to fail early and cheap, whereas biologics tend to fail late and at great cost. The tendency is to move from higher-risk to lower-risk opportunities over time. We've seen the venture capital industry do exactly that over the last 20 years, leaving drug development for diagnostics, devices, and so on. Not completely, of course, but it is certainly harder to find money for a drug project today than it was in 1995. I like to think the current trend is toward wellness rather than disease treatment. Helping the body to do its job even better, immuno-oncology being but one example. Gene editing holds the promise of repairing potential problems before they become diseases. This is very exciting.

"Using drugs to return a patient to normal function is incredibly exciting. Many brain diseases are the result of the dysregulation of neurotransmitters and the ability to return the patient to normal regulation by either drug therapy or gene editing [neuro-transformational medicine] could fundamentally change neuroscience."

Comments by Bayer's **Weinand** also recognize a wide variety of options for industry platforms short and long term, with certain standouts among them. "In line with industry forecasts, we expect small molecules and biologics to remain the core platforms in the industry for the foreseeable future. According to forecasts, biologics [defined as antibody, antibody derivatives, and recombinant protein] and small molecules still will represent greater than 80 percent of the market by 2021. Nevertheless, other technologies, such as gene therapy, are outpacing other platforms. We participate in these potentially disruptive technologies. For example, in December 2015, Bayer and CRISPR Therapeutics agreed to create a joint venture named Casebia Therapeutics to discover, develop, and commercialize new breakthrough therapeutics to cure blood disorders, blindness, and congenital heart disease."

Cohen of Corbus shared one example of an alternative platform his own company is exploring. "We will see more of everything, including technologies that are entirely new. In our case, for example, we're focusing on using the body's own endocannabinoid system to modulate the immune system. This has never been attempted before, and the results could potentially change the way we think about how to treat chronic inflammation."

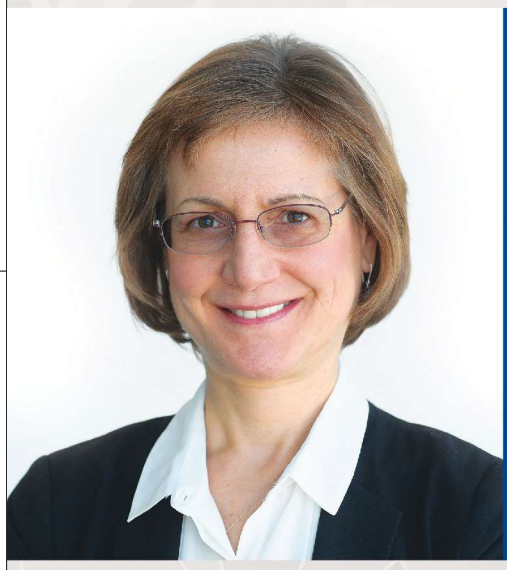
Tetra's **Gurney** focused on emerging platforms in his company's space, "At least in CNS, most drug programs are small molecules or antibodies. Look to increased enthusiasm for oligonucleotide/DNA therapeutics when Ionis-Biogen release their Phase 3 data for nusinersen in spinal muscular atrophy."

STORMY SEAS

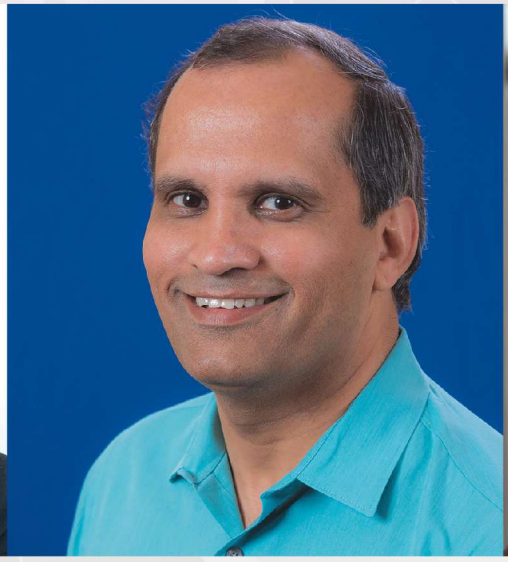
It is good to end on an optimistic note, especially when the earlier responses from the executives portend dangerous waters for the industry in all possible directions next year. As this publication appears, the past and future will have already begun to meld into the moving present, and some of the predictions presented here may have been validated or otherwise by real events. Yet, all together and individually, the contributions from the brave leaders in this forecast illuminate a great deal about how the contemporary industry thinks about the issues of the day — and may it simulate further thoughtfulness in this community.

Can Pharma Build An INNOVATION BUSINESS MODEL For CMOs?

LOUIS GARGUILO Chief Editor, Outsourced Pharma @Louis_Garguilo



JOANNE BECK
EVP Of Pharmaceutical Development And Global Manufacturing, Celgene



SESHA NEERVANNAN
Senior VP Of Pharmaceutical Development, Allergan

DIRK REDLICH, PH.D.
VP Of Technical Development R&D, Janssen Vaccines

The spirit of innovation — the zeitgeist of our times — permeates much of the biotechnology and pharmaceutical industries. But how about outsourcing, and specifically the drug development and manufacturing supply chain? Many pharma sponsors — those we already deem "innovators" — say they need more innovation from their contract development and manufacturing organizations (CMOs).

The trouble is, sponsor-provider relationships in development and manufacturing haven't been set up to accommodate innovation. While there are exceptions, CMOs were founded less around innovation and more on rigorous controls and process replication. That's what pharma has wanted. So now CMOs are leery of this new expectation — some say it's a burden "pushed over the wall" and unto them. The CEO of a CMO said recently, "When you say Big Pharma has changed, I think it's true. Pharma went from saying 'we must invent it here' to 'we can't invent a lot of it here. But you've got to help us with this change.'"

Dirk Redlich, Ph.D., VP of technical development R&D at Janssen Vaccines, understands that sentiment. "We just don't have a better model for incentivizing all parties for what the industry is now talking about," he says. "We're still struggling with finding a model of innovation that fits together to unleash the next level of ideas." He adds, "We are living in complex times, and this is not straightforward. But I see more openness on both sides to at least discuss it."

Discussion is always a good place to start. Along with Redlich, Sesha Neervannan, senior VP of pharmaceutical development at Allergan, and Joanne Beck, EVP of pharmaceutical development and global manufacturing at Celgene, add to our conversation about driving more innovation and new technologies into partner and supplier networks. We'll find out that, as we start turning the pages of calendar year 2017, we'll also be moving through new modes of collaborative innovation in outsourcing.

A THIRD ENTITY OF INNOVATION

Redlich starts us out by describing the current landscape for development and manufacturing. Pharma, he says, typically starts with an internal development group that works out a process, begins scaling up the manufacturing process, and at some point asks, "OK, what's our supply strategy — internal, external, or both?" If there is an outsourced component, the sponsor works diligently on defining specs and transferring a set process to a CMO. The focus is on ensuring that process is run exactly as described by the sponsor.

"But I'm wondering," says Redlich, "whether today we shouldn't, as a matter of course, invite partners in while we are still working out various possibilities. CMOs should be there discussing how to make the process more robust, maybe cheaper, and easier to implement later at the supplier's facility. That's something we haven't fully tapped into: inviting CMOs in to create more value together."

This sentiment has been traveling throughout pharma-dom. Unfortunately, as alluded to above, initial attempts have come off more as a transfer of responsibility to the CMOs than collaborations. "We can't just decide to switch the burden onto the partner," Redlich explains. "We can't just say we expect you to innovate, to become more efficient." He continues, "And what often happens anyway? CMOs come back to sponsors with ideas, and we have to admit it's too late in the project to get 'too creative.' We have to come up with more than mandating, 'Go forth and innovate.'"

The biggest challenge revolves around incentives. Innovation requires investment in human resources, time, capital, equipment, and facilities. "How do you pay for that? How do you incentivize, for example, a supplier to invest in a process efficiency increase, and how do you split the upside?" asks Redlich. "This needs to be figured out; otherwise, why would anybody invest the time and effort?"

What he suggests next takes this partnership for innovation — or value creation, as he'd rather call it — to a level I'd not heard before. He says when the sponsor's product team fully engages with the CMO's, and both are equally empowered early on, the two sides create "a third entity of innovation."

"The thinking changes from 'I'm company A, you're company B,' to combined thoughts on how to create value *independent* of our mother companies," explains Redlich. "In essence, we create a separate body for product value-creation." He calls this a "mentality shift," from thoughts of maximizing the advantages of one company to focusing on creating value for the specific project alone. "That's the way I personally think we grow our business and get real innovation in the future. Therefore, we must work toward a business model that allows for this mindset and then translates that into specific processes and systems, equipment and platforms, and the exchange of information and ideas."

But what is that model?

BOUTIQUES MAY HAVE THE BEST BARGAINS

Neervannan agrees that evolving from the traditional model of fee-for-service to one of partnerships is key to the industry's future. However, he doesn't see a need to overthink this. "Shared innovation can be approached initially from a strict business sense," he says. "You can ask if a quid-pro-quo approach works." He then adds, "No one size fits all, so this model allows for an individualized approach, where the innovators are rewarded with payments for specific innovations. This can then evolve into an ongoing milestone approach, not unlike licensing deals we are familiar with and that are done frequently." But there's still that same caveat: "It does require, though, evolved thinking from both the sponsor companies and the service providers, specifically on how to estimate valuation and come to a mutually acceptable business agreement."

I ask Neervannan if Allergan has been able to make the evolution in practice. "Yes, we've worked effectively with several vendors and partners on novel technologies. We don't apply innovation as a routine selection criteria for CMOs," he further explains, "but it is an important part of our business, particularly where we rely solely on outsourcing. We are increasingly selective in looking for innovative partners, for example when difficult-to-synthesize molecules or unique formulation technologies are needed."

Beck agrees building innovation models starts early and with clarifying the approach to outsourcing from within.

"We're arriving at a balanced view," she says of her company. First, she says, when there's a straightforward project that's easy to outsource, the current model works perfectly well. This is especially true for proven API or drug product manufacturing relationships. Second, says Beck, there are some needs so highly specialized that Celgene doesn't have the full internal capability. "We approach this differently," she says. "We look for a complement from 'boutique' CDMOs." At the same time, "Celgene is also always looking at developing that *internal* capability for these highly specialized platforms, because often we want to develop IP.

"We're trying to apply the right solution to each situation," she continues. "However, there are a growing number of innovators out there that we're interested in partnering with, and the shift has certainly been from, for example, toll manufacturing to long-term development partnerships with CMOs. I do believe most everyone is shifting more toward the CMO that's an innovator or that has special technology — formulation technology being a good example to start with."

But are there enough CMOs currently willing to invest the resources, funding, and efforts in a new partnership for shared innovation?

Neervannan has this take on the current situation. "I believe most large CMOs today are looking for big manufacturing contracts and not so interested in R&D work where more innovation is called for," he says. "At the same time, we too are seeing more boutique companies — mostly in the U.S. and Western Europe — who thrive on this innovation model, and we increasingly seek them out."

What's then the model for this approach? "These relationships are dependent first on mutual trust and respect," he says. "That starts with a big company like mine realizing we want the help from the outsourcing innovator community and taking responsibility for providing the appropriate incentives. We've started using the philosophy of 'open innovation,' a concept that taps innovation from anywhere on the globe, but more importantly provides clear rewards in exchange for solutions to problems. Ultimately, it comes down to recognition and reward."

THE ADVENT OF INNOVATION

But what comes first, a preexisting innovator CMO or the request from sponsors that drives the innovation?

"A little bit of both," says Neervannan. "Typically the CMOs already have the talent, so it comes down to a business agreement to tap that talent appropriately for innovative work. And we also target CMOs with unique technologies already in place that match our specific needs."

Beck says one path to innovation for CMOs is via acquisition. She offers the example of Capsugel acquiring Bend Research to bring in innovative delivery and formulation technology. As she cites her example, I can quickly come up with other CMO-CMO examples, such as Catalent acquiring Pharmatek, predominantly for spray-drying technology, and India-based Piramal acquiring U.S. companies such as Coldstream Laboratories and Ash Stevens, with an eye for high-potency capabilities, among other reasons.

Specifically, Beck sites single-use technologies as a perfect example. "CMOs are picking up innovations that are available out there and introducing them into their facilities. This is very attractive to us, because then we're not feeling like we are developing or manufacturing our products with decades-old technology."

Redlich also mentioned single use as the innovation that has been most helpful at CMOs. "My area of activity is vaccines," he says, "and I'd put it this way — sponsors and CMOs in the biopharmaceutical space have very similar interests here. Single-use equipment works for both sides. CMOs see in this case a clear *financial* rationale to get this technology into their facilities."

While Redlich focuses on vaccines, Beck mentions the manufacture of oligonucleotides. She says the manufacturing technology is still immature, and echoing Neervannan's comments above, she says Celgene actively seeks out boutique firms with specialized capabilities. "There are only so many companies that can manufacture oligonucleotides at large scale and cost-effectively," she says.

Which raises this next question, and brings us back to the need for a business — mostly meaning financial — model for a co-innovation relationship. Does a company like Celgene, for example in the oligonucleotides space, decide to proactively assist a smaller service provider to continue to develop a desired technology?

Beck welcomes the question. "Yes, definitely," she says enthusiastically. But her excitement is for the challenge as much as the opportunity. "This, though, is where you really need to be on the ball," she says of sponsors, "because it now becomes a true partnership, where we leverage their specific technical expertise, and, for example, they leverage our quality systems. Many smaller outfits that we partner with early on won't necessarily have the quality systems to grow into a larger or commercial CMO. We have to invest in them to help them grow."

Going one step further, is there ever the situation where a pharma sponsor might turn to its more-established CMO partner and suggest they acquire a smaller, boutique CMO? "This is certainly not out of the question," Beck replies. So, does she think the large CMOs acquire a smaller company because, for example, they are targeting Celgene's pipeline? Is there a relationship between the sponsor and the CMO before they consider acquiring new technologies? In other words, how do CMOs know what innovation or technology to go after?

"I've seen a lot more CEOs and senior leaders from various CMOs — and I mean well beyond the Lonzas and the Boehringer Ingelheims — start to attend all the industry conferences, participate in leadership and industry technical meetings, present and copresent with their sponsors," replies Beck. "Yes, I do think these relationships between CMOs and sponsors is motivating them to acquire or develop technology. Certainly, we discuss this with partners we've worked with for many years. Also, in this type of partnership, we will actively invest. We don't necessarily want to own a facility and all this equipment; we want to be able to use it when we need it. I think that's a big part of this 'targeted innovation' and new technology model that enables us to develop new drugs for patients, regardless of modality."

DON'T INNOVATE: CREATE VALUE

Let's return to Redlich's defining of innovation as "value creation" and the deriving of new models for co-invention from this concept.

"When we are talking more about value creation, we can see various avenues," he explains. "First, when someone says, 'I can do it cheaper,' what does that really mean? It may mean I can create flexibility in my production plans. We all know that forecasts change, sometimes significantly. How can a supplier anticipate this, be prepared to produce 20 instead of 10 metric tons? That is value creation — creating the flexibility to react to market needs."

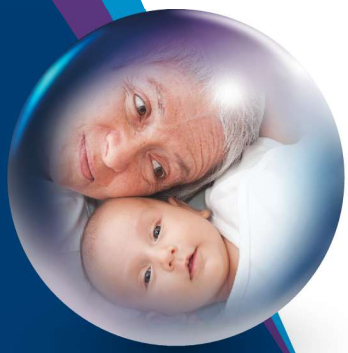
Redlich continues, "Price is only a dimension. In this case, it is defined as manufacturing flexibility. Both parties must consider implementing systems and processes that allow the CMO to be more flexible, to have a leaner change-control process, to be able to move from one product to another, maybe slip in another batch of something. That is value creation. Unfortunately, neither side seems to know yet how best to approach this. For me, single-use equipment is not an example of systems and processes, but of minimizing changeover times, of creating flexibility."

Redlich believes that the fundamental question is not what should pharma expect from its suppliers in terms of innovation, but rather, "How do we design the processes to create opportunities on the supplier side?" "In a way," he says, "there are no answers outside of the relationship. I mean that pharma must do more internally to create those opportunities for innovation. This is collaboration from early on by ensuring you think about processes in the sense that you are optimized for working with your partner." His company has begun to "carefully strive to create processes early on that use lower volumes, or reduce investment costs, not only internally but also externally. We carefully think about whether these processes can be optimized for our partner's multi-use facilities."

THE INCESSANT INNOVATORS

Drug development and manufacturing — along with quality controls, precise replication, consistent and reliable delivery, and strict regulatory compliance — are also part intuition, inspiration, and innovation. And in fact our industry has always progressed by way of science and technologies newly minted from both the brains and brawn of talented men and women. This has manifested over centuries. Just recently we've seen breakthroughs in hepatitis treatments, ADCs (antibody-drug conjugates), new development platforms, single-use equipment, and continuous-flow manufacturing. In a sense, what we see today is pharma's logical expansion of innovation potential to the external and extended supply chain.

That's what innovators do — incessantly look to raise the total real value of goods and services that can be produced for given inputs. Now the focus is squarely on the outsourcing business models needed to accelerate and enhance these potentialities. Who among us doubts that our industry will succeed in coming together to build these new models for co-innovation and value creation? With industry experts like Redlich, Neervannan and Beck, it's getting harder to bet against the march of rapid progress.



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Why 2017 Is The Year To Watch *Biosimilars*

ANNA ROSE WELCH Editor, BiosimilarDevelopment.com @OnBiosimilars

The U.S. pharmaceutical industry entered 2016 with one biosimilar, Sandoz's Zarxio (filgrastim). Now, approaching 2017, the U.S. has seen the arrival of its newest biosimilar on the market, Pfizer's Inflectra (infliximab), as well as the approval of its third (etanercept) and fourth (adalimumab) biosimilars. The EU, which currently has 20-plus biosimilars approved, continues to see marketing authorization application submissions and varying levels of biosimilar uptake among its member countries. According to GPhA CEO Chip Davis, biosimilars have been deemed the top growth driver for the pharmaceutical industry in 2017. But there's still a long way to go before the industry sees widespread uptake of biosimilars. As such, stakeholder education to build confidence in these treatments remains a primary goal for the industry in 2017. In addition, the complexity of the legal landscape and the payer system, specifically in the U.S., will be prime challenges facing companies planning to bring a biosimilar to market in the upcoming year. From a policy and political standpoint, the biosimilar industry promises to be anything but dull in the year ahead. Six biosimilar industry experts told us why.

What biosimilar trends should companies be paying attention to in 2017?

Cheryl Schwartz

General Manager,
U.S. Biosimilars, Pfizer

"We fully expect to see growing acceptance of biosimilars, driven by increased competition, the emergence of real-world experience, and the availability of additional data. For example, results of the NOR-SWITCH study [a two-year Phase 4 study conducted in Norway] delivered outcomes from the first randomized controlled trial to compare the effect of switching from the originator product Remicade (infliximab) to the biosimilar Inflectra. The NOR-SWITCH study adds to the weight of evidence regarding the ability to switch stable patients to Inflectra. Further questions about switching patients from an originator to a biosimilar still need to be addressed, but this evidence will help build provider and patient confidence in biosimilars in 2017 and the years to come."

Alpna Seth, Ph.D.

SVP And Global Head Of The
Biosimilars Business Unit, Biogen

"In Europe, hospitals and healthcare systems are increasingly interested in gainsharing, in which the savings seen from biosimilar uptake may be shared between payers and hospitals, or within departments. I believe we will see more gainsharing efforts across Europe as these systems look to save healthcare costs and better leverage those savings to patients."

David Dunn

U.S. Practice Lead And Scientific Advisor;
Portfolio And Licensing Professional
Services, Thomson Reuters

"The payer dynamics in the insulin space are indicative of a changing attitude toward innovation and biobetters. A major part of innovators' strategies is to develop next-generation versions of their products. These efforts ensure that a biosimilar of the existing product is obsolete when it comes to market.

However, CVS' choice to eliminate Lantus and the next-gen Toujeo from its 2017 formulary signals to companies they have to show their new products confer significant medical benefits that justify the higher costs."

Pankaj Mohan
CEO, Oncobiologics

"In 2017, companies will attempt to differentiate their biosimilars through pricing strategies, delivery devices, and new formulations. Players will likely focus efforts on improving auto-injector pens and making formulation changes that could be handled within the 351K pathway."

Steve Lydeamore
President, Apobiologix

"On the legal front, the biosimilar industry will continue to address the issue of the 180-day notice of commercial marketing. Currently, biosimilar makers are required to wait 180 days before launching their biosimilar products after receiving regulatory approval. Apobiologix and Sandoz have each petitioned the Supreme Court, which has delegated the case to be reviewed by the solicitor general. The Supreme Court will likely wait for the solicitor general's opinion before deciding to take these cases. I expect in 2017 we will continue to hear more about the progress of these cases toward the Supreme Court, as this 180-day wait for market release is a barrier to savings for companies and providers."

Alex Kudrin
Biopharmaceutical Consultant

"As sponsors make concurrent submissions to the U.S. FDA and the European Medicines Agency (EMA) for monoclonal antibody biosimilars, it will be interesting to see how regulatory requirements evolve. It might be the case that some sponsors will be able to obtain approvals based on similarity assessments of quality attributes, in turn, enabling future entrants to develop new biosimilars using smaller and smarter clinical development programs."

Will Company Size Matter In The Biosimilar Market?

Today, the biosimilar industry comprises a wide mix of players, including small pure-plays and biotechs, and big-name brand companies boasting expansive biologics portfolios. The U.S. and E.U. have both seen great developments from smaller companies well on their way toward regulatory submissions and approval. But, in the U.S. in particular, the first four approved biosimilars are emerging from the pipelines of bigger brand companies Sandoz (Novartis), Amgen, and Pfizer. Even Basaglar, the follow-on biologic to Sanofi's Lantus, is expected to be launched this month by Boehringer-Ingelheim and Eli Lilly. The predominance of large companies in the biosimilar market raises some concerns to Alex Kudrin, currently an independent biopharmaceutical consultant, who previously held positions with Celltrion, the Medicines and Healthcare Products Regulatory Agency (MHRA), and Takeda.

"The biosimilar industry is taking the shape of an oligopoly favoring a few large players that are capable of making substantial investments in manufacturing and clinical development," Kudrin argues.

Indeed, larger companies possess greater financial resources, as well as extensive experience in the biologics manufacturing space. These companies also boast a large, global presence, which can serve as a benefit when facing regulatory demands for clinical trials requiring considerable pools of patients.

According to Kudrin, embracing abbreviated clinical development programs with biosimilars will encourage success for a wide range of companies. "Transforming the regulatory pathways so emphasis is placed on fingerprint-like similarity will reduce the size of clinical studies, as well as development costs," Kudrin describes. "In turn, the biosimilar market will see a more diverse range of companies, greater competition, and improved supply chain security."

As the market grows larger, it's also likely the industry will see more partnerships. Oncobiologics CEO Pankaj

Mohan homes in on the list of biologics facing patent expiration in the next 10 to 15 years. "The increasing number of potential candidates will not only challenge companies financially, but will strain development and manufacturing capacity," Mohan explains. Moving into 2017, companies will need to expand chemistry, manufacturing, and controls (CMC) capacity in order to prepare for the second and third wave of biosimilars on the market in 2022, 2023, and 2024. Mohan expects biosimilar makers will accomplish this by establishing partnerships, or through acquisitions.

"It will be more beneficial for companies, both large and small, to work as a team," says Mohan. He also expresses hope more generics players, currently sitting on the sidelines, will jump into the biosimilar space as blockbusters reach their patent expirations.

Pricing, Commercialization Coming To A Head

It's impossible to have a conversation about biosimilar pricing without referring to Norway's infamous 70 percent discount for Remsima (infliximab). Indeed, it was this stunning discount that helped the biosimilar win over 90 percent of the infliximab market share in Norway.

Despite the success of biosimilars in Scandinavia, most countries — and especially the U.S. with its nascent biosimilar market — are far from implementing such extreme discounts. Sandoz's Zarxio and Pfizer's Inflectra were released to market with 15 percent discounts, though U.S. payers have said they expect a 30 percent discount when companies come to the negotiations table. This is in line with pricing in Europe, where discounts fall within the 30 to 40 percent range.

However, there are a few well-known voices already telling the biosimilar market to brace for Norwegian-style biosimilar pricing to come to the U.S. Both Novartis CEO Joe Jimenez and Sanford Bernstein Analyst Ronny Gal have predicted impressive — and daunting — 75 percent biosimilar discounts.

But Thomson Reuters' David Dunn asks the million-dollar questions: "Will that steep of a discount be sustainable? Will companies really be able to make a business out of biosimilars if high discounts become the norm?" The pharma industry is already experiencing intense pricing pressures from payers, politicians, and patients. As Dunn describes, a 15 to 20 percent discount might not provide enough motivation to payers to switch patients from their favorite brands.

Dunn expects larger manufacturers, with more financial security, as well as more established brands, currently stand a better chance at competing in the pricing battle. "Innovators can implement multiple marketing strategies and still retain revenue and maintain market share," Dunn explains. A well-established brand

carries a lot of weight, and patients are loyal to these brands. "This loyalty puts real pressure on smaller biosimilar developers to approach and work with payers to get past the brand loyalty barrier to biosimilar adoption," said Dunn.

Over the past few years, biosimilar makers have faced the technical challenges of developing and manufacturing biosimilars. There have also been challenges establishing the regulatory framework, especially in the U.S. "There's obviously still work to be done on the pathway," Dunn acknowledges. "But testing the regulatory framework will not be the challenge of 2017. We're now moving into the world of commercialization."

Markets To Watch For Biosimilar Growth

When asked which markets, besides the U.S. and EU, would be growth markets for biosimilars in 2017, the experts left no stones unturned. The countries on their radars include Canada, Australia, South Korea, Japan, the Middle East, and the BRICS nations (Brazil, Russia, India, China, and South Africa). According to Oncobiologics' Mohan, the BRICS nations will become major players in the space because of the great need for affordable biologic treatments, as well as their large populations.

Apobiologix's Lydeamore also made a convincing case for the Middle East. There are some differences in terms of how countries approach biosimilars and generics. But Saudi Arabia, in particular, is a branded generics market, so companies market their generics to doctors to garner prescriptions. As Lydeamore explained, "Marketing biosimilars in this country is similar to marketing generics through physicians there, so, as a company, we feel particularly comfortable moving into that space."

But the market that drew the most interest this year is China. Known for its process innovations, the country has proven to be a key market in the generics space. But, according to Pfizer, the space is ripe for biosimilar growth in 2017. Pfizer's Cheryl Schwartz described how the country has introduced a series of reforms encouraging the pharma industry to tackle the rise in noncommunicable diseases and an aging population. This was one of the reasons the company is at work on a new global biotechnology center in the country.

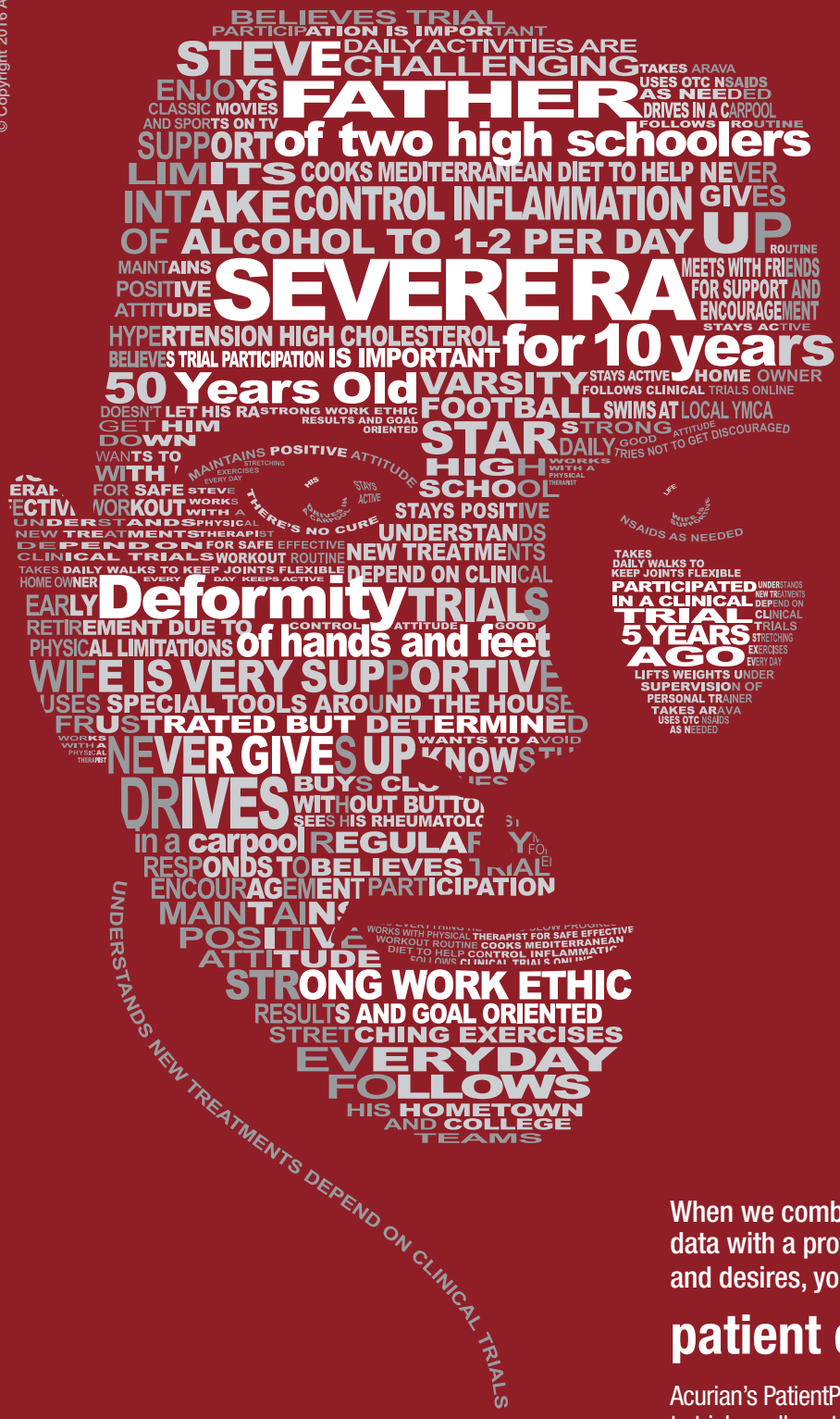
Similarly, as Dunn describes, China also boasts a large, increasingly affluent population, and the use of biologics in the country is on the rise. "I'm interested to see the role Chinese manufacturers will play in the biosimilar market," offered Dunn. "I have no question Chinese manufacturers have the capabilities to enter the biosimilar space. But that's a decision they need to make. Are they going to capitalize on those capabilities? Are they going to become suppliers to the rest of the world, or are they going to stay within China?"

Interchangeability: A Global Question In 2017

In 2015, Australia's Pharmaceutical Benefits Advisory Committee (PBAC) made the momentous decision to recommend biosimilar substitution at the pharmacy level. But elsewhere, interchangeability remains an unclear regulatory standard. For one, the U.S. is still awaiting guidance from the FDA, which is now expected sometime before the end of 2017.

In the 2016 *Life Science Leader* Outlook article, one expert questioned if the FDA would continue down the path of granting biosimilars full extrapolation to all indications. Four biosimilar approvals later, questions about the FDA's willingness to extrapolate are less prevalent. But questions about interchangeability are on the rise. Because the industry has yet to see an official guidance, there's no saying if interchangeability will apply to a product as a whole or if it will be indication-specific. It also has yet to be determined if the FDA's guidance will address interchangeability from biosimilar to biosimilar. Similarly, there are concerns interchangeability could require more clinical data. "Does the benefit of having interchangeability outweigh the downside of potentially having a longer timeline for developing a biosimilar product?" Lydeamore asked.

In Europe, the EMA has left it open to member states to establish their own interchangeability guidelines. However, Biogen's Alpna Seth expects to see this evolve over the next year. She notes the EMA's dedication to releasing guidance on naming and labeling, much like the FDA. "As more biosimilars are approved, and there is more confidence in their use, I believe we will begin to see member states further outline guidelines for switching patients from an originator therapy to a biosimilar," said Seth. For example, she homes in on how some regulatory agencies, for instance, Finland, have provided guidelines to help physicians as they switch patients from originators to biosimilars. L



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PATIENT INSIGHTS LEAD TO IMPROVED PROTOCOL DESIGN

ED MISETA Chief Editor, Clinical Leader @EdClinical

In preparing for this trends issue of *Life Science Leader*, there were numerous clinical topics I could have discussed. Many new technologies are emerging that will change how trials are conducted and impact everyone involved in the process. All of them are deserving of attention. But one long-standing issue that refuses to go away is patient recruitment and retention. For pharma to make headway in this area, build trust with patients, form partnerships with advocacy groups, and get feedback from patients incorporated into protocol design, patient-centricity must continue to be a priority in 2017.

While most pharmaceutical companies would agree that gaining insights from patients is a priority, figuring out how to best acquire that feedback remains a challenge. How do you find patients to query? What questions should you ask? Should you administer surveys or conduct simulations? How involved should you get in a patient's life while trying to gain those insights? If there is one thing we know for sure, it's that patient-centricity officers will have their work cut out for them.

While some companies try to figure out how to answer these questions, others are moving forward with innovative ideas and interacting with patients in new and novel ways. In this article, I look at two companies taking patient-centricity to new heights, and showing others what can and must be done to hear patients and solve recruitment challenges.

Abeona Therapeutics Puts Focus On Patient Travel

Mucopolysaccharidosis MPS III, also known as Sanfilippo syndrome, is a group of four genetic diseases, referred as MPS IIIA, MPS IIIB, MPS IIIC, and MPS IIID. It is a lysosomal storage disorder, and children afflicted with MPS III are missing the enzyme needed to break down long chains of sugar molecules. The result is cells unable to fully break down and replace HS, a material necessary for building connective tissues. Infants and toddlers may not show signs of the disease, but as more cells are damaged throughout the body, symptoms gradually appear. There is progressive neurological and physical decline, including speech, walking, eating, difficult behavior, and sleep issues. This regression continues to full loss of speech, walking, and the ability to feed oneself, leading to a severely shortened life span.

When Abeona Therapeutics began preparations for a clinical trial of MPS III patients, another challenge arose: Children and parents would have to travel to Nationwide Children's Hospital in Columbus, OH, where the trial would be conducted. Some might choose to drive, but because of the location, others would have little choice but to fly. Lodging would also be required for the estimated five weeks that families would need to stay in Columbus on their initial visit, in addition to subsequent follow-up visits.

Discover The Concerns Of Caregivers

Before starting the enrollment process for this trial, Michelle Berg, VP of patient advocacy for Abeona, wanted to understand what the travel experience was like for the children and their parents. She felt the best way to gain that understanding was to engage and interact with a handful of families. Her hope was to understand the specific challenges they faced when traveling by plane or by car, and staying for an extended period of time in a city that's unfamiliar and potentially far away.

"We had certain assumptions going in, based on what we had learned in the past, but it was amazing to hear input from the families on everything from how to arrange seating on an airplane to what type of accommodations would be most convenient," says Berg. "The interactions took place via teleconference, and we selected families with children of different ages and different regions across the country. The teleconferences also included caregivers of patients with both MPS IIIA and MPS IIIB (two of the four types of Sanfilippo syndrome). These caregivers have jobs

> “These caregivers have jobs and are being asked to uproot their families for an extended period of time.”

MICHELLE BERG
VP Of Patient Advocacy, Abeona

and are being asked to uproot their families for an extended period a time. We wanted to make what is surely a stressful experience as positive as possible.”

Regarding the flight, Abeona assumed that a seating location near the front of the plane, as close as possible to the exit, would be preferable. That assumption was correct, as it facilitated a quick boarding and off-boarding experience. But something the company hadn’t considered was the placement of caregivers. Berg found families had a preference for placing one caregiver or parent in the seat directly in front of the child, instead of seating everyone in a single row.

“That was a bit of a surprise, but after talking through it, we understood why,” says Berg. “These kids have behavioral challenges and might kick or pound on the seat in front of them. This could irritate the passenger sitting there and make for a stressful situation for the parent(s). It’s difficult to stop the child’s behavior, but placing a caregiver in that seat can alleviate an uncomfortable situation. The exit row also provides additional leg room for children over the age of 15.”

Another preference was bulkhead seating, if available. Having a panel in front of the child, rather than a passenger seat, allows both parents/caregivers to sit next to the child during the flight.

Safe And Comfortable Living Space

The next concern was lodging. Since trial participants and family members would be spending several weeks in Columbus, the facilities had to be both comfortable and accommodating. Because of the extended stay, rooms with a kitchenette were preferred, as they allowed families to eat in rather than dine out at a restaurant every night. Caregivers also preferred a site close to the hospital so as to minimize travel time.

Berg was able to locate a suitable apartment facility near Nationwide Children’s Hospital with the help of the Batten Disease Support and Research Association, a local organization working to support families impacted by all forms of Batten Disease, another area of focus for Abeona. It was selected based on both location and proximity to certain amenities the families indicated would be helpful, such as parks, grocery stores, and retail shops. Abeona selected a two-bedroom, two-bath unit that also happened to be handicap accessible. It includes a full kitchen, in-unit laundry facility, balcony, and living room, and was fully furnished by Berg and some helping hands. Even Tim Miller, Ph.D., CEO and president for Abeona, got involved by hanging curtains and assembling furniture.

Additional modifications still had to be made to the apartment to make it safe for the children. Berg put a lot of additional thought into this, as well as soliciting feedback from caregivers.

Because the children may have hyperactivity or sensory limitations and will be staying in an unfamiliar environment, their safety was a primary concern. Abeona took all of the furniture with sharp edges, such as tables and stands, and placed padding on the edges. Another concern was children pulling heavy objects upon themselves. For that reason, items such as televisions and lamps are securely mounted to tables and walls to prevent them from being moved. Other miscellaneous items in the apartment (soap dishes, for example) were selected on the basis of containing nonbreakable materials and rounded edges. Locks were also placed on doors to prevent kids from making unplanned escapes.

“In the apartment we also installed blackout draperies, because sleep can be another challenge for patients and, therefore, caregivers,” adds Berg. “Having the room as dark as possible will help create a better sleep environment for everyone.”

Pfizer And Ethnographer Focus Camera On Patient Lives

Sickle cell is a disease that affects both men and women via their hemoglobin, the molecule in red blood cells that delivers oxygen throughout the body. Patients with the disorder have atypical hemoglobin, which distorts red blood cells. Although it can affect any race, it is much more common in the African American population.

“The red blood cells with the abnormal hemoglobin will collapse into a sickle shape,” says Brenda Cooperstone, VP and chief development officer for rare diseases at Pfizer. “These cells bump up against the blood vessel wall, causing endothelial damage. That, in turn, starts a cascading effect in terms of inflammation and blocking of small blood vessels. This results in terrible pain which can occur anywhere but is often felt in the bones.”

Other symptoms of sickle cell include anemia, repeated infections, strokes, and lung clots. But pain is the greatest challenge, and patients can be faced with the onslaught of a pain crisis at a moment’s notice. As a result, it can be uncomfortable and very disruptive to patients and caregivers.

Patient Recruitment Raises Concerns

In 2011, Pfizer entered into an agreement with biotech firm GlycoMimetics to develop Rivipansel, a molecule for the treatment of vaso-occlusive crisis in sickle-cell patients. Per the agreement, GlycoMimetics would take the treatment through a Phase 2 trial, and Pfizer would be responsible for all future development. Although the treatment produced hopeful results in a Phase 2 trial, Pfizer knew performing a Phase 3 trial would not be easy. It took GlycoMimetics three years to recruit just 76 patients for the Phase 2 study. For the Phase 3 trial, Pfizer would need over 300.

"We knew we did not have nine years to recruit them," says Cooperstone. "None of us wanted to wait that long to bring what could potentially be a life-changing medication to these patients. We knew we had to do something different, and felt a good place to start was with an understanding of the patient community.

Cooperstone did not know much about the sickle-cell community, but she did know many of these patients were not willing to participate in trials, and retaining them in studies was also a challenge. If she was going to partner with them to advance a clinical program, she needed to understand their condition and needs.

Look Into Patient Lives For Insights

To help with that understanding, Pfizer contracted with an ethnographer who had access to sickle-cell patients. Ethnographers study people and cultures, and she was someone who could get to patients, insert herself into their lives, and see what it was like to live with this disease. By viewing a video of their journey, Pfizer could design and conduct a trial that would be more conducive to patient participation.

Pfizer received hundreds of hours of tape, which was watched by Cooperstone and members of the development team. That team included up to 15 individuals including clinicians, medical monitoring physicians, statisticians, and staff from market research and development. Much of the footage showed patients experiencing their episodes of pain and the treatments received. Footage also included patients being interviewed about their experience with the healthcare system and the treatments they received.

"The videos brought us very specific insights about what we could do differently to enroll this trial faster," says Cooperstone. "One of the things we concentrated on was the vernacular. For example, we noticed these patients never refer to what they were going through as a vaso-occlusive crisis, even though that's both the medical and regulatory term used to describe it."

That simple finding was important to Pfizer, as the material it had, including the protocol and all patient-facing materials, referred to the situation as a vaso-occlusive crisis. Physicians, investigators, and other healthcare providers know the term, and assumed patients would know what they were talking about. The videos clearly showed patients were not familiar with it at all, instead referring to it as a crisis, pain crisis, or simply pain. The experience changed how investigators refer to the crisis and led Pfizer to change the wording in its materials.

> "The videos brought us very specific insights about what we could do differently to enroll this trial faster."

BRENDA COOPERSTONE
VP And Chief Development Officer For Rare Diseases, Pfizer

Preplanning Helps Recruitment

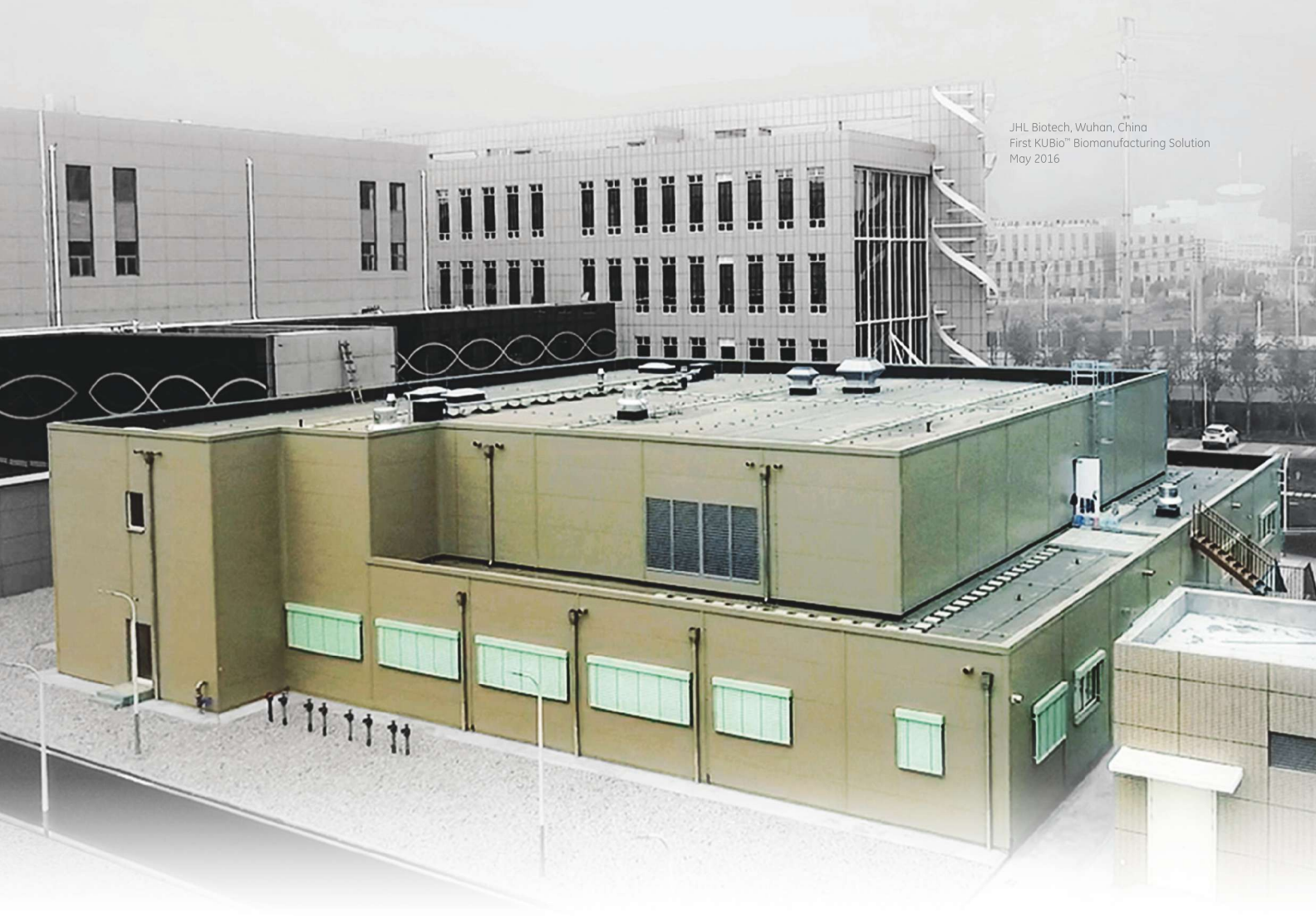
A second discovery was far more telling. Patients are generally placed into a trial and randomized to receive either the treatment or placebo when they are rushed to the emergency room with a pain crisis. Unfortunately, when patients are in that situation, Cooperstone notes they are in no condition to make important decisions.

"When in the middle of a crisis, they are in absolutely no shape to go through an informed consent process," she says. "In the Phase 2 trial that recruited 76 patients, these individuals were in the emergency room, writhing in pain, with someone in front of them requesting informed consent. After listening to patients, we knew that had to change the way we consent patients."

In the current Phase 3 trial, patients can be brought in and informed of the consent process prior to the onset of a crisis. An investigator will go through the informed consent form and all of the study procedures, after which the patient can agree to participate. By signing the consent form at that time, patients simply reaffirm the consent when they enter the emergency room.

Transportation was also an issue, since individuals participating in a trial would have to be taken to the correct hospital. With the early consent process in place, Pfizer could arrange for that transportation. Today, patients who consent to the trial have an app installed on their phone. When they have a pain crisis, the app will send a text message to a transportation service that delivers them to the correct emergency room.

"For us, that emergency room visit was where patients entered the trial and became a partner with Pfizer," adds Cooperstone. "We knew it was the place where we needed to make improvements for both the patient and sites. Without some of the positive outcomes we put in place, it would have been very difficult to get patients to become part of the trial and receive the treatment they needed." L



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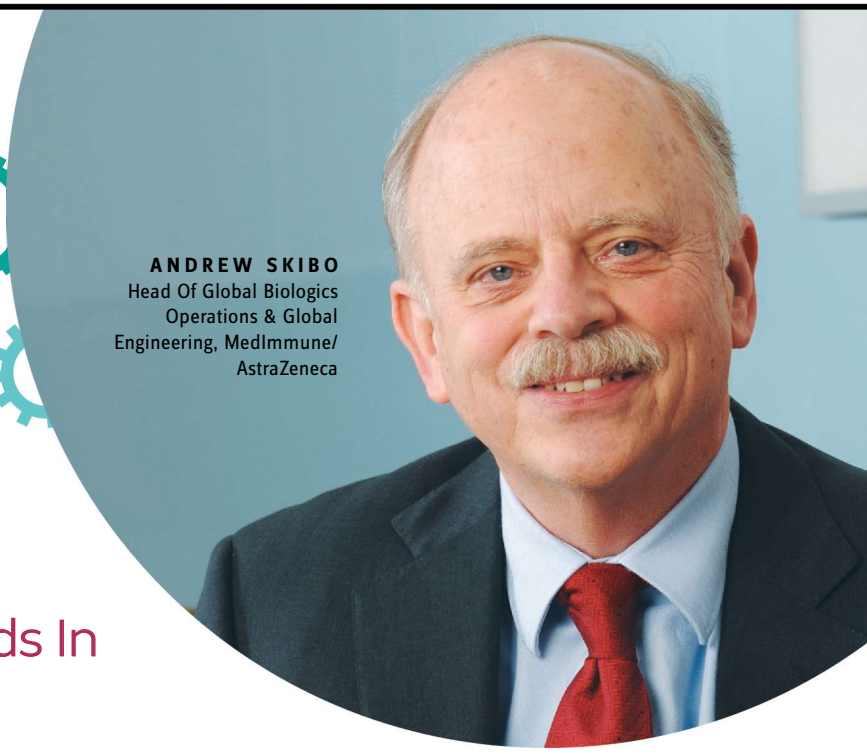

ANDREW SKIBO
Head Of Global Biologics Operations & Global Engineering, MedImmune/AstraZeneca

What Are The Key Trends In

GLOBAL BIOPHARMACEUTICAL MANUFACTURING For 2017?

ROB WRIGHT Chief Editor @RFWrightLSL

Over the years, *Life Science Leader* magazine has covered key manufacturing trends taking place in the biopharmaceutical industry. For example, we have seen a rise in manufacturing outsourcing, so much so, that we actually created a series of education events to help CMOs and sponsors collaborate more effectively (i.e., OutsourcedPharma Conference And Exhibition). We developed awards programs (e.g., the data-driven CMO and CRO Awards) and publish special supplements to help with the process of selecting an outsourcer, while recognizing the best of the best.

For this article we asked biopharmaceutical manufacturing experts, who also serve on *Life Science Leader* magazine's editorial advisory board, what key manufacturing trends we should be paying close attention to in 2017 and beyond. You will find their thoughts interspersed as sidebars throughout this article. This is because we view one of the most important trends (i.e., biomanufacturing capacity, or the lack thereof) as a focal point. But don't take our word for it. One of the people on the front lines of this topic is Andrew Skibo, head of global biologics operations & global engineering at MedImmune/AstraZeneca. This past May, Skibo chaired a series of presentations at the ISPE Global Pharmaceutical Manufacturers' Leadership Forum in Frankfurt, Germany, during which he highlighted the significant changes taking place in the biopharmaceutical supply chain. Essentially, Skibo is concerned that industry might not have enough biomanufacturing capacity to support the world's increasing demand for biologics — despite the *unprecedented* nearly $20-billion expansion currently in planning or actual development. Since his initial presentation, Skibo has given the same speech at a number of additional venues. In addition to the concern that we might not have enough capacity, there is also the potential, if not properly coordinated, for biopharma to overbuild, and it might soon face a situation similar to that of the oil industry (i.e., overcapacity). Skibo sat down with *Life Science Leader* to share why he sees biomanufacturing capacity as a key trend that demands your attention.

Bracing For The Biomanufacturing Capacity Crunch

Describe The Manufacturing Capacity Issue As You See It.

The bio industry's large-scale manufacturing supply is very constrained. While drug product is just beginning to become an issue, drug substance is effectively sold out. About six years ago I was at a manufacturing forum, where many of us seemed to be working in environments with surplus capacity, and there was a lot of financial pressure to consider closing or selling plants. A number of us compared notes, and knowing our pipelines, could see the surplus capacity window closing somewhere in 2017. Because of all the red ink being generated during this surplus manufacturing capacity time period, it was doubtful any board of directors would have approved a biomanufacturing expansion, and why, perhaps, we find ourselves in this current strained-capacity situation.

What Are The Variables Contributing To This Biomanufacturing Capacity Crunch?

There are three:

- Companies with broad biologic pipelines
- The rise in biosimilar manufacturing for novel biologics going off-patent
- Larger than anticipated patient populations for new biologics.

Unlike the 1980s and 1990s where most companies' futures were determined one product at a time, those active in the biologics space have fairly broad pipelines, which, if successful, will require increased and perhaps diverse means of manufacturing to support.

Though some anticipated biosimilars being a big biomanufacturing capacity sinkhole, this has turned out not to be the case, thus far. That being said, none of us anticipated the impact of some of the new spaces, such as immuno-oncology (IO), which we probably underestimated by at least three times over. So, while biosimilars demanded less than expected, products like the IO mentioned or PCSK9 inhibitors filled in the biomanufacturing capacity gap at a rate much larger than expected. To understand the scale that is rapidly approaching biomanufacturing, imagine if just one Alzheimer's drug makes it to market. To meet the demand of tens of millions of patients could require a plant seven times the size of AstraZeneca's 710,000-square-foot (i.e., 16 acres) facility in Frederick, MD (depending on the product and specific indications). In other words, many companies involved in developing biologics are suddenly facing needing two or three additional plants.

Now That We Are Seeing More Biosimilars Gaining FDA Approval, How Might That Further Exacerbate Biomanufacturing Capacity Demand?

It is definitely going to be a factor. Some companies (e.g., Samsung, Boehringer Ingelheim) will really be key when it comes to providing capacity to meet biosimilar demand. By 2020 and onwards, biosimilar manufacturing could represent at least 10 percent of some companies' total global biomanufacturing capacity.

What quality manufacturing trend do you anticipate having the biggest impact on the biopharmaceutical industry in 2017?

In quality manufacturing, the biggest impact can be made in areas such as reporting real-time production metrics and developing product analytics platforms. The days of assuring manufacturing quality based on "after-the-fact" measures are over. Today's pharmaceutical industry environment is ever volatile, with escalating drug shortages, growing regulatory requirements, pricing debates, globalization, and forecasting and planning challenges. Companies will need to recast their quality and manufacturing approaches to stay competitive. It is critical to transform manufacturing thinking to incorporate metrics and predictive analytics in order to drive improvement in manufacturing productivity, flexibility, efficiency, and quality. Being better informed with metrics and predictive analytics can position leaders and managers to better anticipate quality failures over the product life cycle. The potential return on investment through early identification of areas for continuous improvement is where the true impact can be made. Fewer production defects, less unplanned downtime, leveled inventory, and reduced material waste can provide a much higher reinvestment into pipeline development and R&D efforts. Therefore, a quality-centric culture is where it should begin to drive innovation and to gain the edge in a competitive landscape.

Jason Urban, Ph.D.
Senior Director Of Global Quality Operation, Celgene

What manufacturing trend do you anticipate having the biggest impact on the biopharmaceutical industry in 2017 and beyond?

Sandra Poole
EVP Of Technical Operations, ImmunoGen

We are living in a world of rapid change, increased interconnectivity, complexity, and uncertainty. The forces of change and pressures on our technical and manufacturing operations are enormous – from pricing pressures and increased competition to technological, regulatory, and social changes. These trends are forcing an accelerating evolution in our manufacturing operations. The introduction of new technologies is changing plant designs, plant support systems, and even work practices. Global supply chains are becoming increasingly more complex as we seek to manage therapeutics produced in new biologic platforms while ensuring their global delivery into highly variable local conditions. Add to this the shifting workforce demographics that are challenging leaders to manage different values and expectations of a multigenerational workplace.

Unfortunately, today's manufacturing leaders lack the essential leadership skills to effectively manage in this undulating landscape. If this isn't bad enough, the methods we have been using to develop our leaders (i.e., static one-directional, lecture-style delivery of best practices based on past experience) have not kept pace. Further, most leadership development programs, with the standardized one-size-fits-all curricula, are not designed to cultivate the key leadership attributes/capabilities necessary for the future – adaptability, self-awareness, and innovative critical thinking.

However, exciting advances are being made and new approaches being introduced which are beginning to address the leadership gaps. One example is the use of *action learning* methodologies where leaders immediately apply and integrate their newly learned skills to their "real work." Other examples include developing deeper self-awareness through coaching and making time to learn from mistakes. These types of leadership development opportunities are daily and ongoing. How are today's leaders learning from the successes, challenges, and setbacks their team, plant, or network experiences? What adjustments are they making as a consequence of these new learnings? Do they have the ability to critically assess the outcome of that adjustment and then lead their team or organization through the institutionalization of the learning? These are the questions we should be asking and the trend we should first be seeking to address. For all the "cool" trends of continuous manufacturing and other shiny tools won't mean much if we (i.e., manufacturing leaders) don't have the essential skills to lead in today's world.

Empirically, What Is The Projected Scope Of This Manufacturing Capacity Crunch?

There is nearly $20 billion worth of large-scale biopharmaceutical site projects currently being planned or already in progress. Some are two- and three-phase exercises. However, $13 billion of these remain in the very early stages of development, meaning we are way behind as an industry. If you add up the bioreactor capacity that will be part of these projects, it's greater than 1.7 million liters of large-scale, terminal capacity. That doesn't include any of the small-scale capacity needed for high-titre, smaller demand products.

Anecdotally, How Do You Think Industry Stakeholders Will Experience This Biomanufacturing Capacity Crunch?

Currently, biopharma manufacturing executives are either being pressured to build, which most major firms are pursuing as a partial strategy, or secure guaranteed contracts with major CMOs to ensure biomanufacturing capacity. But these aren't the typical size CMO contracts. For these major buys of capacity demand, you are seeing biopharmaceutical companies taking a significant part of a new plant that CMOs are building. Two or three years ago, a large European CMO was debating whether or not to build a new 4x15,000-liter plant. Today they are in the process of building a 9x15,000-liter facility. And while this is great and could help, because of the length of time it takes to bring one of these plants online, we won't see a measurable impact on alleviating capacity demand until somewhere between the years 2021/2022.

Could Companies Seeking To Lock Down CMOs For Guaranteed Capacity End Up Causing Drug Shortages Of Other Products?

Where that risk will occur will be at conservative companies that don't move quickly enough to implement such contracts. I have never seen such competitiveness in trying to lock down CMO capacity. Just trying to find five lots worth of capacity at the 15,000-liter scale at a

CMO, short of the year 2021, is currently a real challenge. Keep in mind that these are costly commitments, and if your timing is wrong by a year, you could be explaining to your CFO why you spent $50 million for a year's worth of manufacturing capacity you didn't need.

But, thinking a little more about your previous question, I would like to add that there are several factors exacerbating the possible drug shortage issue. One is with the new approval processes (e.g., breakthrough therapies, accelerated approvals). Another is the rapidity with which science is moving. The old cycle time of six to seven years from concept to approval has shortened to three years, and neither you nor a CMO can build a fully validated and operational large-scale biomanufacturing facility in this shortened time period. In addition, part of your risk management strategy today includes trying to plan for capacity of as of yet unknown products. For example, if your company commits to discovering two Biologic License Applications (BLAs) a year, those responsible for biologic manufacturing capacity have to allow for two BLAs per year that don't yet exist. That's a new planning paradigm. Another thing driving manufacturing demand uncertainty is the sheer size of new markets. Even in late-stage development for certain therapy areas (e.g., IO), and I would argue post-launch, the demand band can be 5 times what was anticipated. How do you plan for that? When going before the executive committee to seek project approval, I believe it is as important to seek corporate understanding of the "white space" capacity that you are consciously not planning to build as it is to seek approval for what you are planning to build. And if you get that equation wrong on the low side, because CMOs as previously mentioned are already capacity constrained, you may find yourself (during these lean capacity years) not being able to provide product.

Could We See CMO Price Gouging As A Result Of Such Competitiveness?

That is a small part of the overall pharma equation. While we wouldn't welcome CMO prices going up by 25 percent, such an increase wouldn't have a material impact on what we do as an industry. My bigger worry is that most CMOs are developing their own novel pipelines, as well as biosimilars, which have much better margins than traditional outsourcing contracts. And if a CMO's pipeline projects prove successful, they are going to need at least some (if not all) of that capacity. In other words, we could see that using CMOs to try to manage our way through this biomanufacturing capacity crunch becomes even more difficult. Though they will have to honor these contracts, when it comes time to renew in 2022/2023, we may find CMOs much less willing. Further, when you have a product that's licensed in 80 countries, it's not easy to move it from one CMO facility to another, assuming another CMO even has available capacity.

What Is Necessary To Realize The Promise Of Advanced Therapy Medicinal Products

When *Life Science Leader* posed the question, "What might have the biggest impact on the biopharmaceutical industry in 2017?" to editorial advisory board member Charlene Banard, SVP of global quality and technical operations at Shire, rather than fire back her opinion, she sought the counsel of others throughout her organization. "Unsurprising, a variety of trends cropped up," Banard stated. "Responses ranged from device software applications and other regulated product supplements to continuous manufacturing and deployment of the FDA's quality metrics program. But our industry's proclivity for innovation and sometimes forgotten lessons of the past led me to share the thoughts of my colleague, Thomas Kreil, Ph.D., the head of Shire's pathogen safety organization."

Advanced therapy medicinal products (ATMP), such as gene therapy, somatic cell therapy, and tissue engineering, hold the promise of making treatment available for as yet unmet medical needs. Technological progress during recent years has been rapid, and regulators in the U.S. and elsewhere are establishing or refining procedures to escort these products to market. Yet in some ways, ATMPs are quite normal biological medicinal products, fraught with some of the same issues that history has witnessed for plasma derivatives, and later recombinant proteins: the exposure to universally present and uniquely effective opportunistic agents (i.e., the microbiological environment).

Thomas Kreil, Ph.D.
Senior Director Of Global Pathogen Safety, Shire

To ensure the innovative power intrinsic to ATMPs does not get stigmatized by earlier-faced complications, the development community is well-advised making use of the most advanced technological approaches to safeguard them from exposure to pathogens. For an unfortunate reminder of realities, the manufacturing platform of a licensed ATMP has already been found to be contaminated with a virus, fortunately this time not pathogenic to humans. Technologies that may be applied to safeguard ATMPs include, for example, next-generation sequencing for the characterization of innovative cell substrates, microbial barriers for microorganisms now effective against even viruses in the upstream rather than traditionally in the downstream process, and consequently closed or functionally closed downstream manufacturing processes to minimize any exposure to operators and the environment. Altogether, ATMPs may bring about a bright future, with treatment possible for many still-orphan conditions; if only we do not forget the learnings from the past.

What Happens If Companies Get Biomanufacturing Capacity Planning Wrong And Overbuild?

While most of us expect processes to improve by two to three times, we are not building as much capacity as today's yields require. We assume we will get better by the time these plants go online. There is a real risk to a possible industry overbuild. And though we are all doing our best to risk-adjust while still planning for success, some biopharmas won't have the successes for which they had hoped — a reality of biopharmaceutical discovery. These unpleasant surprises will arrive somewhere around 2022. Some companies will have a plant come online that won't be utilized as anticipated. The converse will also be true, as the bands of risk for new biologics with primary care-sized patient populations will have some companies on the low side of being able to supply market demand. Many of us are asking, "Should we, as an industry, really be building this much?" Years ago I remember sitting on what felt like an ocean of manufacturing capacity. Michael Kamarck, Ph.D., my biologics counterpart at Merck, and I were at a forum discussing an industrywide capacity issue. That conversation led to the eventual execution of the Merck-AstraZeneca capacity-sharing agreement known as the Trusted Partner Network (TPN). While this was probably the first time in the industry where two companies actually shared biomanufacturing capacity, it is likely we will see many more similar capacity-sharing initiatives in coming years.

So, What Advice Do You Have For Biopharmaceutical Manufacturing Executives?

I suggest folks be a lot more introspective and less conservative when planning for biomanufacturing capacity demand in the next five years. This will be easier for large firms with broad pipelines, because if some of those biologics don't hit, they can always lay off some of those risks on other products. For smaller firms with only one or two biologics, this could be much more difficult, especially if some of their pipeline has the potential to be big. All firms will need to watch a spectrum of risk profiles and try

to not get overcommitted. But when looking at a take or pay option of a product with a projected market of $2 billion, a $50-million-a-year contract with a CMO might feel expensive if the market doesn't materialize. On the flip side, imagine walking into the C-suite because there is no other capacity available and trying to explain why you can't supply that extra $2-billion worth of biomanufacturing capacity. It's not just the lost revenue and the bottom line. These are specialty care products, and there are patients and human lives tied to that $2 billion in product that can't be supplied. Such situations are what end up on the front pages of newspapers, and you will have wished you had spent the $50 million and not needed it, than face a scenario of not being able to supply.

How Are You Addressing This Capacity Crunch At Your Organization?

We are investing significantly, both internally and externally. We have expansions at our Frederick, MD, facility ($213 million), which will add significant new small-scale, high-titre capacity. We bought Amgen's Boulder, CO, drug-substance facility a year ago for $14.6 million, and we will have it commercially online in 2017. We also recently acquired Amgen's Longmont, CO, campus for $64.5 million, which will not only support the Boulder facility, but provides room if we decide to expand Boulder or build another plant. We are building a new drug product facility in Sweden ($285 million) that will be online by 2018/2019. Finally, we will have engaged our CMOs in long-term contracts that provide additional capacity. In total we have invested about $600 million. As for how we are mitigating the risk, we've tried breaking these capacity expansions apart into digestible pieces that can be staged. Telling the CFO that you have no choice but to build a plant twice the size of the Frederick, MD, facility at a cost of $1.2 billion, and that you need to start right away, isn't very palatable. Splitting demand apart into five and six stepwise pieces allows us to stage adding capacity so we aren't asking for all the money in just one or two years.

Any Other Advice?

Watch out for nonmammalian-cell platform capacity. Some products aren't going to fit on mammalian-cell capacity. As such, it becomes even more prudent to quickly figure out where to find that capacity. Microbial, for example, is not a big piece of everybody's pipeline, so that type of platform capacity is rarer. There are a few products that demand profusion, which is another rare form of capacity. If you have a nonplatform technology, one thing companies haven't always been good at doing (until they get bigger) is working with their development colleagues to make sure (in the earliest stages) that they understand what platforms can be easily worked on. If possible, plan for trying to keep this on platform technology, and be instantly aware of those that aren't platform so you can immediately start planning from where to get supply.

Lastly, if you haven't already done so, start having some cross-network discussions. These will help build an industrywide biomanufacturing planning picture and provide for sounder judgment while weighing internal-capacity decisions.

What biologics manufacturing trend do you anticipate having the biggest impact on the biopharmaceutical industry in 2017 and beyond?

I am anticipating we will see increased standardization of single-use systems (SUS) and how we manage them. Standardization has the potential to reduce costs, shorten lead times, and improve quality. Rather than focusing efforts on process and product development, engineers are currently engaged in customization of SUS, management of orders, and other off-target tasks. It is typical for biopharmaceutical manufacturers to individually expend resources tackling challenges related to design, qualification, and testing of SUS. These challenges are common, and many of them are not points of competition. Joint efforts to develop standard processing platforms, standard modules for fluid management activities, standard test methods for systems qualification, and standards for communication should be pursued by industry groups made up of both suppliers and SUS users. Efforts such as the collaborations between BPOG (BioPhorum Operations Group) and BPSA (Bio-Process Systems Alliance) to develop user requirements, specification templates, and change-notification standards are a great start. An emphasis on standard systems with standard quality expectations will allow suppliers to optimize manufacturing methods and biopharmaceutical manufacturers to focus on process development and optimization. This will lead to improved quality and reliability of SUS and the processes and patients that depend on them.

Mark A. Petrich, Ph.D., PE
Director, Single-Use Systems Engineering, Merck; Second Vice Chair, Bio-Process Systems Alliance

DRUG-DELIVERY DEVICES

Could Be A Big Winner In 2017

BOB MARSHALL Chief Editor, MedDeviceOnline.com @MedDeviceOnline

Where is the medical device industry headed, and what factors will shape it in 2017? First, we should not underestimate the macro-level effect the presidential election will have on policy and regulation in 2017. Since the day after the votes were tallied, many voices in and around the medical device community have been asking big questions. *Will the Affordable Care Act be changed or eliminated? Will the medical device tax be repealed? Will there be more industry-friendly leadership at the FDA and CMS?* The answers to these questions have huge potential impacts, but they will be realized only after the new administration is in place. Those answers will shape market size, the cost of doing business, speed to market, and the ability to get paid. With this uncertainty, what can we do? We can focus on things that are more predictable, at least to a panel of industry experts. We spoke with three professionals "in the know" to garner their insights on topics such as market drivers, positioning, and growth opportunities.

NIC BOWMAN

Senior Director, Head Of Devices CoE, Pfizer Limited, Cambridge UK

What market drivers will most influence drug delivery devices over the next two years?

Given the time frames for delivery, the launches over the next two years will have already been defined by now, or the underlying technology (if a platform device) will be predeveloped. Over a longer time frame, the market trends appear to be influenced by several factors, including improved usability, improved patient preference, reduced pain, and the potential for connectivity.

How should companies position themselves to address those issues?

A clear strategy should be defined for ongoing development. The strategy should be informed by knowledge of the competitive landscape, patient preferences, new technology available, the company portfolio, and the regulatory environment.

What types of devices/delivery platforms offer the most market growth opportunity?

Differentiation is required to enable patient preference to play a role in prescribing in a complex multiplayer market, which is increasingly becoming the norm. Adding device options to capture the broadest patient grouping is viable and has been demonstrated in the diabetes market, but not replicated in other therapeutic areas to the same degree.

Which therapeutic areas will lead to the most growth in delivery device?

Clearly, home-use chronic therapies are the main driver for delivery devices. The holistic cost benefit of self-medication with the home environment is a strong driver for many franchises. Although there are clear current leaders (diabetes, rheumatoid arthritis, MS), there is no overriding reason why other franchises should not migrate further into this space. There are already examples of switching intravenous to subcutaneous to enable more convenient delivery for the patient.

Pharma/bio companies have shifted their business model from acquiring a device to developing delivery devices in-house. What trends will emerge in purchasing, outsourcing, or partnering of devices, versus in-house design and development?

A number of development models still exist, ranging from fully outsourced to full internal development. All models have benefits and compromises. Of the 23 disposable auto-injectors launched since 2006, 20 were developed with external partners, so the evidence is that external partnerships still make up the most significant proportion of developments. Device companies are playing a strong role in development; their business models are now changing to include the development of fully tooled device options to enable very fast times to the clinic.

Do you anticipate a growth in the drug industry's partnerships with consumer electronic and technology companies?

Connectivity is creating a growing "buzz" of interest and enthusiasm across the industry. Technologically, this is quite achievable, but no one has established a viable system that covers all the open questions. An industry

consortium would be one way to potentially enable definition of an industry broad standard to allow development of systems that are suitable for all parties, including patient, pharma, payers, and healthcare professionals.

How will today's empowered patient (aware, engaged, and making decisions) drive change in delivery device considerations?

The importance of the patient in the choice of therapy is becoming recognized. When a choice of delivery device is available within a therapeutic area, it is clear that the patient could have an influence on the brand that is prescribed. Hence, it is important to understand patient preference, and design your devices to suit.

MAX CAMBRAS
Life Sciences Expert,
LEK Consultants

What market drivers will most influence drug delivery devices over the next two years?

First, there is increasing competition from brands, biosimilars, and generics. This leads us to believe we're going to see more insulin-like markets going forward. More and more, the administration experience is going to be a basis of competition. We're even seeing oncology become relevant in this discussion. In the past, differentiating based on the administration experience in oncology would have been unheard of.

Another trend is going to be the more frequent use of specialty medicines in spaces that have been traditionally served by small molecules. We're already seeing this in hypercholesterolemia, and we're going to see an increase in specialty medicines in migraine and asthma and in other areas where we previously just had oral small molecule formulations.

That's going to create a device dependency in these markets. It's also going to introduce devices to patients who are pretty naïve when it comes to using such devices. And it's going to make the demand for the user experience that much more complex.

When you reference "specialty medicines," are you just talking about refinements or are you referring more to precision medicine?

It's a little of both. I think it's really about introducing protein therapy use. We're going to see protein therapies entering areas where they haven't played in the past. There's going to be protein therapies, for example, in asthma beyond Xolair, and those therapies are going to be self-administered.

Will these changes bring a whole new set of problems as well?

Sure, there will be a lot of issues to work through regarding self-administration. Whenever you're talking about self-administration, you have to discuss device simplicity and usability. You have to address these two issues if you want to broaden the range of applications.

After the fact, you're going to see formulation work in tandem with devices to improve the user experience.

How should companies position themselves to address these issues?

It really depends on the company's specific pipeline and the markets they're focused on. We appreciate that some companies want to try to be "fast followers." However, I don't know how rational that point of view is considering the current standing of combination product legislation.

I understand that not everybody wants to be at the front line of innovation. I do think, though, that most companies need to seriously assess how they're going to participate in delivery innovation going forward. Otherwise, they're going to be left behind by companies that have already embraced it.

Biopharma is traditionally not very good at device design. At those companies that are innovating, the device groups need to take ownership over the historic disconnect between device engineering and commercial. They'll need to bridge that gap and create a really tight coupling.

What types of devices/delivery platforms offer the most market growth opportunity?

There are exciting device platforms that are going to drive growth. This is certainly the case in wearables — wearable bolus injectors, wearable micro-infusers. Recently, Amgen launched one in the PCSK9 space with West Pharmaceuticals that was the first of its kind. We'll continue to see wearables grow in importance as they become easier to use and more competitive with auto injectors — more set-and-forget — and potentially more comfortable for the user.

I also think with soft-mist inhalers and piezo-type nebulizers, you'll see a change in the classic metered-dose and dry-powder inhalers (MDI/DPIs). That's not to say those are going away, but the soft-mist inhaler that's out there now is an improvement over MDI/DPI. And I expect others to try to adopt similar platforms (e.g., integrating device with digital/connective technologies).

Is the soft-mist inhaler designed to allow other drugs to be delivered that way, or is it just a more comfortable, effective delivery method?

With the right development work, it may be able to do both. And I know that biopharma is looking for it to do both. One of the reasons is the issue with the lack of well-behaved antibodies. Both the piezo and the soft-mist have the potential to deliver protein therapies without destroying them. With the jet nebulizers, if you put anything in there, it just wipes it out. All you can put in there are the small molecule chemicals.

Also, if you look at it from the small molecule perspective, you really get better penetration into the

lungs. With both types, there's a lot less product left in the mouth and throat, and also it's a more comfortable experience to get that soft mist than to get the blast from either a jet nebulizer or MDI/DPI.

JIM COLLINS, PE, MBA

VP, Device Development Unit, Sanofi

What market drivers will most influence drug delivery devices over the next two years?

I see two elements that are going to be important. First is the role that connectivity could provide with integration into delivery devices to impact health outcomes.

Second is the role of the payer and payer access to healthcare formularies. With more biosimilar products — or therapeutically equivalent products — there's a good opportunity for devices to differentiate, but there's also the potential for a diminishing of the role of devices if the payers don't make more than one device option available to the patient.

How should companies position themselves to address those issues?

In addition to patient-centered design, it will be important to have an element of what I'll call payer-centered design. Patients don't benefit unless they get access to the product. The roles that device product costs play and how the payers provide access are critical to understand in the design process.

Regarding connectivity, building out med tech capabilities, having the ability to integrate electronic and embedded software, as well as partnering with key external companies in this space will all be important going forward.

What types of devices or delivery platforms offer the most market growth opportunity?

If you look at the market data, large molecules today are delivered by the patient primarily in only four device types: auto-injectors, prefilled syringes, infusion systems, and pumps. Overall, the growth in auto-injectors is substantial, and we should anticipate it will continue, not only with monoclonal antibody delivery, but because more peptides and proteins are being engineered to be delivered weekly.

Then, what I see is that some aspect of large-volume injection, patch injectors, or body-worn injectors will emerge as an opportunity, because when you get above a certain milligram level, it is difficult to deliver in an auto-injector the total drug volume in the delivery time that regulatory authorities and patients are requiring.

For small molecules, pulmonary/respiratory and transdermal devices make up the lion's share of the market. I expect those will continue to be the key areas to focus on and will provide the primary opportunities for growth.

Do you think in emerging markets it'll be the same trends, or will there be different delivery mechanisms?

In emerging markets, cost is more of a factor. I think we could see prefilled syringes become a key mode of delivery in emerging markets. But the challenge for pharma companies — and I think this is a challenge that can be achieved — is getting the development and manufacturing costs of pens and auto-injectors down to where they can be made available for emerging markets on a broad scale.

Of course cost will continue to be a driver in established markets, too. We need to think about how to design low-cost solutions for emerging markets and actually apply them on more of a global basis.

What are some top challenges facing drug delivery device companies and professionals?

I haven't talked much about patient-centered design because it's now almost core to what everybody's doing. But it still is key to the design process. You need to be patient-centered and really understand the difference between patients, because RA patients are different from those with diabetes, and so on. You also have to design *the system*, not just the device. The delivery system can only be optimized if the drug substance, formulation, primary container, and device components are all designed as a system to meet the patient's needs.

We have to figure out how to engage R&D and others on the patient experience seven or eight years before the product's going to market. That's a challenge. How do you best teach a biopharma research organization that it is very important to be thinking about the patient administration experience from the very beginning if they really want to optimize the product.

Device leaders in biopharmaceutical companies have to realize that their job is to figure out how to make the process work end to end. You can't just think that your device design role is to take the baton from point A to point B, because if you do, you're never going to be successful. You have to try to influence and improve the entire device development system within your company end to end.

This doesn't mean you have to own device manufacturing, marketing, or medical, but it means you have to be able to influence from discovery all the way through manufacturing and into the market. You need to work to educate everybody from medical to marketing to legal on what their role is to make a successful device, and to help them build business processes you need to successfully develop those delivery devices. If you don't do that, it's really hard to put yourself in a strong position to succeed. L

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How Resilient Are You?

Machiavelli's Advice

JOSEPH L. BADARACCO

JOSEPH L. BADARACCO is the author of the new book, *Managing in the Gray: Five Timeless Questions for Resolving Your Toughest Questions At Work*. He is the John Shad professor of Business Ethics at Harvard Business School, where he has taught courses on leadership, strategy, corporate responsibility, and management in the school's MBA and executive programs. His other books on these subjects include *Defining Moment*, and the *New York Times* best-seller *Leading Quietly*.

Machiavelli is known as the high priest of sleaze. His big idea was supposedly that the ends justify the means — and any means are OK. But ask yourself a question. Would we even know Machiavelli's name today if all he said was you can get ahead by being sleazy? This has been known since ancient times, and you probably know someone who got ahead, in part, by cutting corners ... or worse.

Machiavelli's enduring idea was something different. He said that leaders had to develop plans that would work in the world as it is. Put differently, leaders who aren't pragmatic and realistic about how the world really works will fail themselves and the people who depend on them.

What is "the world as it is"? For Machiavelli, it was very much like our world today. It is a world of intense competitive pressure, smart people pursuing their self-interest, and lots of surprises, good and bad. In this world, responsible leadership requires resilience. You have to be resilient and so do your decisions and plans.

What does this mean in practice? I've studied, taught, and observed executives for years and focused on how the best leaders make uncertain, high-stakes decisions. As I see it, resilience means you have to ask and answer questions like these:

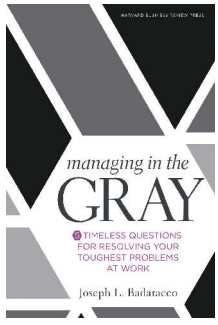
1. **DO I UNDERSTAND THE FORCE FIELD OF POWER AND INTEREST AROUND ME?** In other words, have I thought realistically about who is likely to support my plans and who will oppose them? Have I thought about how much clout these parties have? In other words, who wants what and how successfully can they pursue it?

2. **AM I BEING MODEST ABOUT HOW MUCH I KNOW AND HOW MUCH I CAN CONTROL?** When you make gray-area decisions in an uncertain world, you have to remind yourself that often the best thought-out plans can easily be upended. It's important to follow President Eisenhower's advice: "Rely on planning, but don't trust plans."

3. **AM I READY TO BE FLEXIBLE AND OPPORTUNISTIC?** Machiavelli is typically viewed as a pessimist, and he did advise people to watch their backs. But a fluid world has happy surprises, and this means you have to be ready to modify your plans and seize unexpected opportunities.

4. **AM I WILLING TO PLAY HARDBALL?** Generally, the best way to get things done is with analysis, persuasion, and goodwill. But sometimes leaders face persistent dissent or outright opposition. When this happens, you have to be ready to assert your authority — diplomatically but clearly. You have to be willing to say: "I've made a decision, this is what we are going to do, this is why, and I expect you to help us move ahead."

5. **ARE YOU TEMPTED BY THE EASY WAY OUT?** Machiavelli praised the entrepreneurs of his era. They were changing long-established ways of thinking about politics, art, human nature, and business. This is why he said, "Fortune favors the bold." Resilience means taking prudent risks, shaking the tree a little, and seeing what you can accomplish with courage and determination. L



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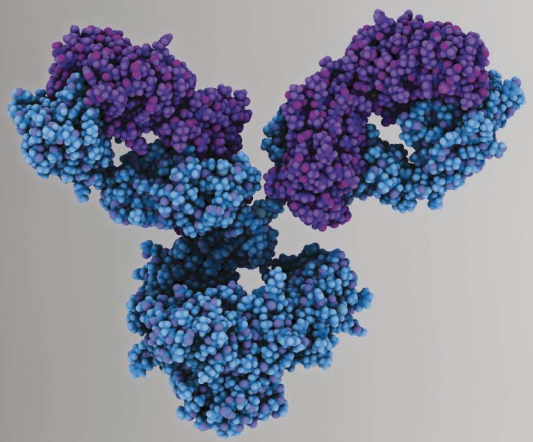

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