SPECIAL ISSUE

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DECEMBER 2017

2018 INDUSTRY OUTLOOK

For transfusion decisions made in real-time, don't you need real-time data?

SpHb noninvasively provides continuous visibility to changes in hemoglobin, which may help clinicians make more informed and timely transfusion decisions.

Peer-reviewed studies have found that using noninvasive SpHb monitoring in conjunction with invasive blood samples has helped clinicians to:

Reduce Unnecessary Transfusions

in low blood-loss surgery:

> 87% reduction in transfusion frequency (from 4.5% to 0.6%)[1]
> 90% reduction in average units transfused (from 0.1 to 0.01 units per patient)[1]

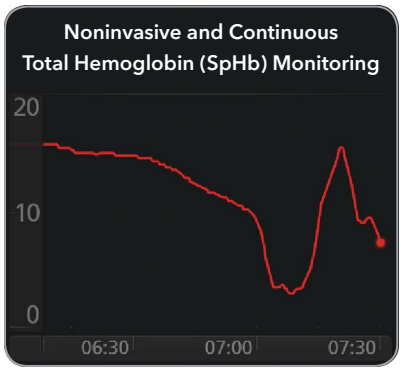
in high blood-loss surgery:

> Reduction in the percentage of patients receiving 3 or more units from 73% to 32%
> 47% reduction in average units transfused (1.9 to 1.0)[2]

Initiate Timely Transfusion When Transfusions Are Needed

in high blood-loss surgery:

> Transfused an average of 41 minutes sooner[2]



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[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9. [2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4.

Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyzer.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information, including indications, contraindications, warnings, and precautions.

Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering among other factors: patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples. SpHb monitoring is not intended to replace laboratory blood testing. Blood samples should be analyzed by laboratory instruments prior to clinical decision making.

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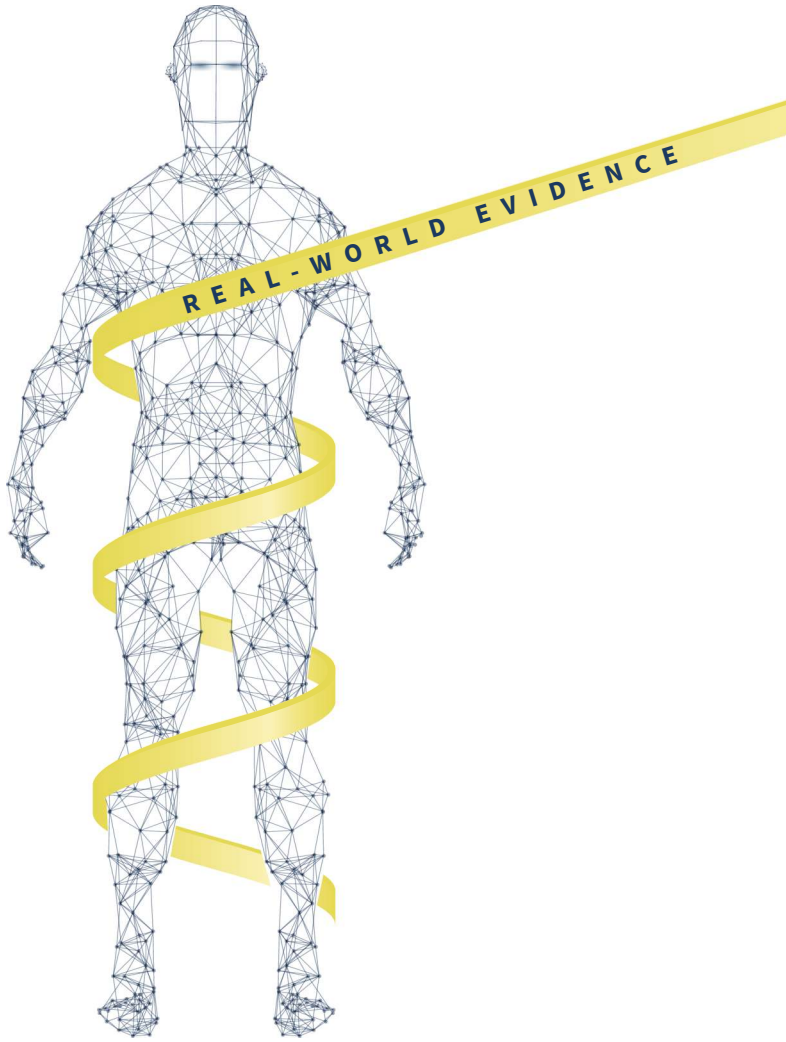

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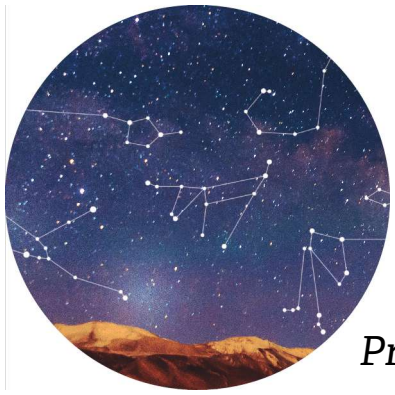

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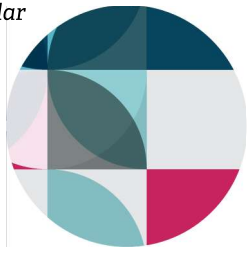

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Back To The Future

ROB WRIGHT Chief Editor

The sci-fi movie classic *Back To The Future* came out about a month after my high school graduation — a time when I was very focused on my future (which seemed so bright I had to wear shades – ba-dum-bum-CHING). In *Back To The Future II*, released shortly after my graduation from college, movie characters Marty McFly and Doc Brown time travel to Oct. 21, 2015, when, supposedly, we'd have a host of crazy new technologies and products. While the movie did miss on its prediction of the Cubs winning the World Series (by one year) and a few other things (e.g., flying cars), it proved pretty accurate on some of its other forecasts, such as personal drones, tablets, mobile payment technology, biometric devices, and smart clothing, just to name a few.

I admit I have always taken pleasure in pondering what the future might hold and thus relish opportunities to watch TED Talks or read books by futurists like Ray Kurzweil. So when John Cumbers, Ph.D., and Karl Schmieder asked if I'd be willing to preview their book, *What's Your Bio Strategy?* prior to publication, I was all in. The book interviews 25 innovators about what the future may hold and the important role to be played by biologics — beyond just drugs. For instance, I learned about Modern Meadow, which is growing leather without using an animal; Glowee, which is developing living lighting energy via bioluminescence; Ginko Bioworks, which is engineering crops that can fertilize themselves; and Bolt Threads, which is harnessing proteins found in nature to create fibers and fabrics and has already produced a spider silk tie. The book also discusses concepts such as using DNA for data storage, how the future of fashion may reside in garments being grown in vats (i.e., biofabrication), and oh so much more.

One of the people interviewed in the book is biopharmaceutical billionaire, R.J. Kirk, the CEO of Intrexon, a company that has dazzled us with nonbrowning apples, cloned kittens, and genetically modified mosquitoes to fight the Zika virus. Kirk is but one of an unparalleled number of biopharmaceutical industry thought leaders participating in this year's annual outlook issue. From the biggest of Big Pharma (Alex Gorsky, CEO of J&J), to generic powerhouses (Heather Bresch, CEO of Mylan), and just about everything in between, this year's CEO outlook feature *is* bigger, better, and more diverse than ever. Our manufacturing outlook article alone has 10 thought leaders taking part. And while we are thrilled to have CDER director Dr. Janet Woodcock involved this year, we are grateful to all the manufacturing executives who honored their commitment to take part, despite the adversity many continue to face following Hurricane Maria's devastation of biopharmaceutical operations in Puerto Rico. We hope you enjoy this year's outlook issue and look forward to your feedback on what we can do to make next year's even better. L

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LIFE SCIENCE LEADER
5340 Fryling Rd., Suite 300
Erie, PA 16510-4672
Telephone: 814 897 7700
Fax: 814 899 5587

WWW.LIFESCIENCELEADER.COM

CEO
Jon Howland / Ext. 203
jon.howland@lifescienceconnect.com

EDITORIAL DIRECTOR
Dan Schell / Ext. 284
dan.schell@lifescienceleader.com

CHIEF EDITOR
Rob Wright / Ext. 140
rob.wright@lifescienceconnect.com

EXECUTIVE EDITOR
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

EDITORS
Louis Garguilo
louis.garguilo@lifescienceconnect.com

Bob Marshall
bob.marshall@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Anna Rose Welch
anna.welch@lifescienceconnect.com

VP OF AUDIENCE DEVELOPMENT
Michael Bennett
michael.bennett@lifescienceconnect.com

STRATEGIC PARTNERSHIPS/BUS. DEV.
Mike Barbalaci / Ext. 218
mike.barbalaci@lifescienceconnect.com

Tim Bretz / 724-940-7555 / Ext. 123
tim.bretz@lifescienceconnect.com

Cory Coleman / 724-940-7555 / Ext. 125
cory.coleman@lifescienceconnect.com

Scott Moren / Ext. 118
scott.moren@lifescienceconnect.com

Denise Mosley / 724-940-7555 / Ext. 126
denise.mosley@lifescienceconnect.com

Shannon Primavere / Ext. 279
shannon.primavere@lifescienceconnect.com

Perry Rearick / Ext. 263
perry.rearick@lifescienceconnect.com

Ray Sherman / Ext. 335
ray.sherman@lifescienceconnect.com

Tracy Tasker / Ext. 297
tracy.tasker@lifescienceconnect.com

Derek Van Slyke / Ext. 217
derek.vanslyke@lifescienceconnect.com

Casey Weed / Ext. 219
casey.weed@lifescienceconnect.com

DATA ANALYTICS
Rick Miller
rick.miller@lifescienceconnect.com

Kevin Morey
kevin.morey@lifescienceconnect.com

PRODUCTION DIRECTOR
Lynn Netkowicz / Ext. 205
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Q What country (other than the U.S.) will have the biggest impact on biopharma in the next three to five years?

A HAVING WORKED IN PHARMA in the EU, U.S., emerging markets, and Japan, I have found outstanding research and a passion for patients in each of these geographies. Most impressive are the international networks of collaboration and the exchange of ideas that happen between countries. In our business, we must seek scientific excellence wherever it is, oblivious to borders and stripped of preconceptions. Indeed, funding from biopharma is often essential in countries where there are less academic resources. From Glasgow to Hyderabad, there is a desire to replicate the dense clusters of biotech found in Boston and San Francisco with a mixture of biotech, pharma, and academia encouraging cross talk between industry and academia and a fertilization of ideas.

SANDY MACRAE, M.B., CH.B., PH.D.
is CEO of Sangamo Therapeutics. He has over 20 years of leadership experience in the pharmaceutical industry.

Q What disruptive technologies will transform biopharma in the next three to five years?

A I WAS JUST READING A *LIFE SCIENCE LEADER* ARTICLE on Blockchain and its potential applicability to pharma. Although it arose as a way to secure financial transactions, I am hearing more about its applicability to secure technology systems in the tech arena. Although data security is always of concern to pharma, particularly in a clinical trial setting, I do agree that integration of Blockchain into our highly regulated processes will take time. However, if its promise is demonstrated in other industries over the next few years, Blockchain could be a disruptive technology that transforms pharma: everything from the way we perform clinical trials, to the way we assemble documents for regulatory filings, to the way we do partnership deals, to the way we manage supply chains and product sales.

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

Q What innovations will impact biopharma in the next five years?

A I EXPECT WE WILL SEE THE IMMUNE SYSTEM HARNESSED with our growing understanding of the role of T cells and B cells in disease. We already have seen CAR-T therapeutics take off with Kymriah. I expect this will continue with others entering the field. In oncology, immunotherapies stimulate the immune system. The other side of T-cell therapeutics is antigen-specific immunotherapy or epitope-specific immunotherapy designed to selectively shut down or reprogram the specific T-cell response causing autoimmune disease. The expectation is that the immune system is selectively reprogramed so that it does not attack. Failures have been abundant, but the tide has turned, and I expect new treatments entering the market along with biomarkers to monitor disease. Of course, CRISPR technologies and pay-for-performance pricing will continue to evolve and impact biopharma.

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

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Trump Surprises: **340B Reform And Pharmaceutical Exec For HHS**

JOHN MCMANUS The McManus Group

The Trump administration surprised the healthcare community when it stuck to its guns and finalized a proposal to substantially cut Medicare reimbursement of Part B drugs provided to 340B hospitals.

The Hospital Outpatient Prospective Payment System (HOPPS) final rule, issued November 1, will slash Medicare payment to most 340B hospitals from 106 percent of average sales price (ASP) to 77.5 percent of ASP — a 28.5 percent reduction. While the final rule exempts rural hospitals (read: hospitals in Republican districts), children's hospitals, and prospective payment-exempt cancer hospitals, it locks in the reduced payment amount CMS proposed this past summer to the urban and suburban hospitals that drive volume in the program.

Policymakers recently have focused on the 340B program as its size ballooned from $6 billion in 2010 to $16 billion in 2016 and the number of covered entities doubled in that same time period. Whole cottage industries have been created that instruct how hospitals and contract pharmacies can profit from the loose regulations, to the point that the drug industry can no longer overlook the market inefficiencies (Genentech alone has reported billions in discounts to 340B, revenue which must be made up elsewhere). Yet despite several oversight hearings by the House Energy & Commerce Committee, which raised concerns about whether patients were actually benefitting from the discount program, Congress could not come to a consensus on how to reform it.

The American Hospital Association, the powerful teaching and public hospital lobby — with well-connected members and jobs in every district — has grown reliant on this revenue and strenuously opposed program reforms. And many health policy hands were skeptical that the administration would withstand the considerable pressure the hospital industry could exert. They rallied 57 Senators and 228 Members of the House to oppose the Medicare cut proposed by CMS.

But legislative gridlock spurred executive action. Starting in January when the rule goes into effect, Medicare payments to 340B hospitals for outpatient drugs will fall by almost $1.6 billion annually, and Medicare beneficiaries will save about $320 million annually in lower copays, which will be based off the discounted price, not the inflated prices.

However, this payment cut does not result in a net savings to Medicare. The hospital outpatient prospective payment system is budget neutral — meaning these cuts to 340B hospitals for their outpatient drugs are redistributed as higher payments to all hospitals for all other items and services.

The Medicare Payment Advisory Commission (MedPAC) had suggested targeting that redistribution to hospitals that provide uncompensated care. CMS ignored that recommendation and rather increased reimbursement to all items and services by 3.4 percent. This policy will split the hospital community because non-340B hospitals, such as private hospital chains that are not eligible for 340B, will receive a windfall.

Only Congress can remove resources from the payment system through a change in the statute — a very good reason there may be an end-of-year provision trying to capture some of these savings while simultaneously providing some relief to hospitals.

MedPAC had been examining 340B for the past several years and estimated the 340B discounts to be 34 percent below ASP, meaning 340B hospitals are still profiting on drugs reimbursed at 77.5 percent of ASP. Other government agencies estimated even greater discounts from the program. The Office of Inspector General had found that participating providers were paid 58 percent

more than the discounted prices. 340B discounts on some products may be 70 percent or greater, based on price increases since date of launch.

In explaining its rationale for the policy change, CMS says it believes, "based on numerous studies and reports, that 340B participation is not well correlated to the provision of uncompensated care and is associated with differences in prescribing patterns and drug costs."

Anticipating litigation on the matter, CMS included an unusually detailed discussion of its statutory authority, knocking down each argument by hospitals that it lacked the legal ability to execute the policy.

CMS then struck at policy weakness in the hospitals' argument: "The fact that hospitals did not submit comments suggesting an alternative minimum discount that would be a better, more accurate reflection of the discount at issue is instructive for two reasons. One, it gives us confidence that our suggested payment of ASP minus 22.5 percent is, in fact, the low bound of the estimate. ... Two, it gives us confidence that the affected hospital community does not believe there is some other number, such as ASP minus 24 percent or ASP minus 17 percent, that would be a better, more accurate measure."

Where do things go from here? That's unclear. The major hospital industry trade associations have filed lawsuits to block the policy from going into effect but that has an iffy probability of success.

This rule establishes unit-level tracking for drugs acquired under the 340B program. All providers, exempt and nonexempt, will have to report when Medicare beneficiaries are receiving 340B discounted drugs. This data haul should provide real data for additional reforms, which CMS hints at in its verbiage.

The pharmaceutical industry remains stifled by the loose statute and limiting regulatory oversight of the program — currently all patients, regardless of insurance or economic status, qualify for the program if they show up at the 340B hospital pharmacy or its contract pharmacies. The pharmaceutical industry would like the definition of the "patient" substantially circumscribed and targeted at low-income and the uninsured. But even a freeze to the program's ever-expanding nature would be welcome. Both of those policies require legislative action by Congress.

Free-standing physician practices welcomed the payment cut to competing 340B hospitals that often use those resources to buy still more practices. The Community Oncology Alliance said it strongly supports this policy that will "help curb outrageous abuses of the 340B program by some large hospitals, and hopefully, start to reverse the profit incentives that have dismantled our nation's community cancer system."

Yet physician practices are now realizing that the rule contains a loophole, which allows hospital-acquired off-campus practices to continue to receive full ASP+6 percent reimbursement if they are paid for their healthcare services at the physician office rate. This could permit substantial diversion.

ALEX AZAR NOMINATION FOR HHS SECRETARY

President Trump announced a rather surprising nominee for Health and Human Services (HHS) Secretary: former Eli Lilly executive Alex Azar. Surprising because during the campaign, and at intermittent times since then, Trump has characterized the pharmaceutical industry as price gougers who are "getting away with murder."

Yet the choice seems shrewd. Azar served as the HHS General Counsel under the Bush Administration and knows the bureaucracy and policies as well as anyone. He is well-liked and highly regarded. More importantly, he understands the practical policy implications on the private sector for decisions made in Washington. He helped Lilly navigate several challenging years when key products were going off patent and several promising products for Alzheimer's failed to pay off.

Former HHS Secretary Mike Leavitt said, "We worked side by side on the implementation of Medicare Part D, pandemic preparedness, and Hurricane Katrina recovery. He is an expert on health policy and HHS operations, as well as a skilled manager. Because he knows the department so well, there may never be a HHS secretary better able to hit the ground running than Alex Azar."

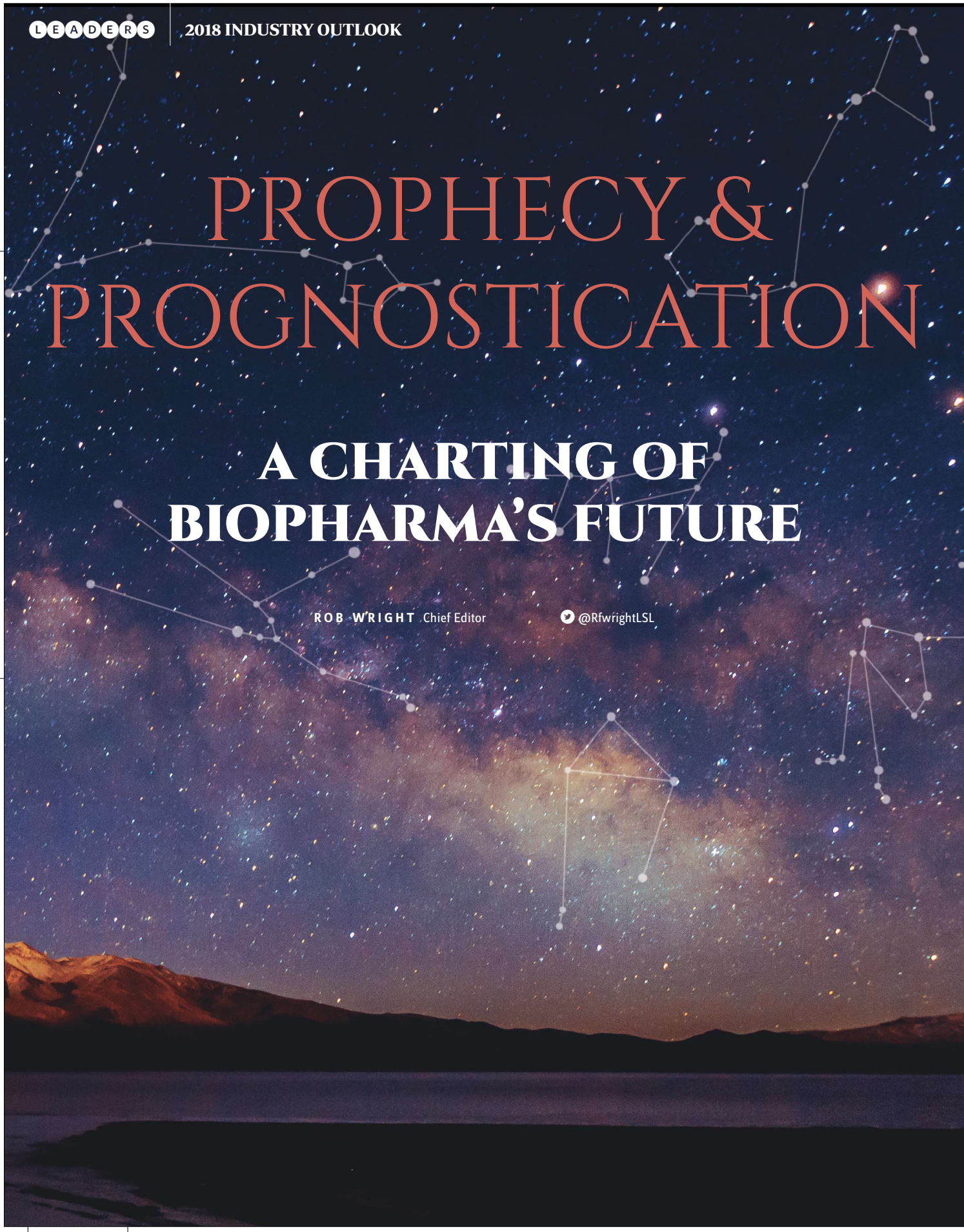
But look for a bruising confirmation fight, with Democrats focusing in on Lilly's price increases of insulin and other products during his tenure. Republicans may argue that no HHS Secretary knows the pharmaceutical industry better than Azar and he has a unique skillset to tackle to complex problems in this sector. 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.

PROPHECY & PROGNOSTICATION

A CHARTING OF BIOPHARMA'S FUTURE

ROB WRIGHT Chief Editor @RfwrightLSL



Predicting the next big trends or business transformations in any industry — much less in biopharmaceuticals — is a crapshoot at best. For instance, at the end of 2016 a lot of experts envisaged at least one CAR-T therapy gaining approval in 2017. Instead, we got two: Gilead's Yescarta and Kymriah from Novartis. But with Kymriah we also got a new approach to drug pricing — a 30-day money-back guarantee. How many had that approach to drug pricing on their radar?

So how do we best predict who or what might have a big impact on the biopharmaceutical industry in 2018? Although there are no guarantees with this kind of prognostication, we felt seeking the opinions of experienced top biopharma executives would be a good place to start. For answers we reached out to a cross section of biopharmaceutical industry CEOs, from the biggest of Big Pharma, to billionaires, to generic powerhouses, and just about everyone in between.

WHAT GLOBAL MACRO TREND WILL HAVE THE BIGGEST IMPACT ON BIOPHARMA IN 2018?

Heather Bresch
Mylan

There is significant unmet medical need in emerging markets. As these countries achieve greater prosperity, they are gaining greater access to medicine. While it's true that economic growth in these markets has slowed, we can still expect growth, just at a slightly slower pace. IMS Health estimates that "pharmerging" markets will spend $330 billion on pharmaceuticals by 2021. Similarly, we can expect populations in India, Russia, and Turkey to increase their healthcare spending over the next five years.

WHAT U.S. MACRO TREND WILL HAVE THE BIGGEST IMPACT ON BIOPHARMA IN 2018?

Jeff Riley
Synthetic Biologics

If the current limbo over tax reform continues, an increasing number of development-stage companies may feel compelled to look at other nontraditional funding sources in 2018. Increased private investment from family funds, private equity, and venture capital, and perhaps even crowdfunding may emerge to fill the delta. One such strategy that may continue to gain traction in 2018 is the newly adopted REG A+ equity offering. REG A+, which stems from the JOBS (Jumpstart Our Business Startups) Act, uses a crowdfunding component that allows private companies to raise up to $50 million from the public markets. Like a traditional IPO, REG A+ allows companies to offer their shares to the public. Unlike traditional IPOs, however, REG A+ allows hundreds of smaller retail-minded investors direct access to a company's IPO alongside accredited investors before shares become available in the secondary markets.

WHAT BIOPHARMA TRENDS DO YOU FIND MOST EXCITING?

Rachel Haurwitz, Ph.D.
Caribou Biosciences

The continued intersection of technology and biotechnology is exciting and critical to the future of our industry. The overlap between these fields is happening in a myriad of ways, including tech entrepreneurs like Mark Zuckerberg and Sean Parker funding major research institutes and cutting-edge companies. Big Data analytics are necessary for our industry's research efforts to understand the increasing volume of sequencing and genomics data we can collect, as well as clinical trial data sets. Tech giants like Alphabet, through its subsidiary Verily, are investing hundreds of millions on new data tools and technologies to better understand human health and inform ways to achieve better health outcomes.

WHAT'S GOING TO BE BIG IN BIOPHARMA IN 2018?

John Crowley, J.D.
Amicus Therapeutics

Our understanding of human genetics, medicines, Big Data, and our overall health will advance dramatically in 2018. The success of gene therapies and precision medicines will continue to accelerate in 2018. I expect major breakthroughs in gene-editing platforms and the introduction of human therapeutics. More people will have their human genome analyzed and interpreted. Clinical trials in many areas, such as rare diseases, will begin to be radically altered to reflect a growing understanding of the role of human genetics in predicting safety and efficacy of new medicines. We will move closer to the dawn of a golden era of medical and biotechnologies.

WHAT WILL THE GLOBAL BIOPHARMA INDUSTRY LOOK LIKE IN 10 YEARS?

Lynn Seely, M.D.
Myovant Sciences

Clinical development, sales, and marketing of medicines will be transformed by Big Data, digital innovation, and artificial intelligence (AI) converging to provide rapid and efficient drug development and, most importantly, precision prescribing. The cumulative impact will be decreased costs as more medicines are quickly brought to market. Data acquisition, aggregation, and analytics will allow more rapid and efficient clinical trials with optimized enrollment criteria, site selection, patient recruitment strategies, statistical powering, and endpoint selection. Remote data collection and telemedicine using a variety of devices will make it much easier for patients to participate in clinical trials, regardless of geography or mobility. On-site source-data verification will become obsolete with most data monitoring performed electronically. Patients will gain information from a variety of credible electronic sources and take more control over their healthcare. The biopharma industry will provide information to physicians, other prescribers, and patients through digital mediums, and sales forces will find themselves in the same category as the rotary phone. In 10 years, the reputation of the pharmaceutical industry will be transformed to one of credibility and respect, as a result of the large number of clinically meaningful drugs brought efficiently to market at prices justified by patient benefit.

WHAT INNOVATIVE COMPANY OR PERSON OUTSIDE OF BIOPHARMA DO YOU PAY ATTENTION TO?

Mitch Gold, M.D.
Alpine Immune Sciences

Elon Musk has been the most innovative person outside of biopharma who's taken a lot of personal and reputational risk to advance the electrification of America. He recognized that it's not about the car; it's about bringing power to the people in the form of innovative new battery technology. Initially, it wasn't obvious why he'd merge Tesla and SolarCity, but when you think about electrifying the home and the storage challenges, it makes sense to combine capturing energy with solar panels and storing that energy locally with the Tesla wall battery. Musk believes the future of the world requires humans to be a multiplanetary species. As such, he founded SpaceX and is leading the charge of tackling this hugely audacious goal. Do we have anyone thinking this big in biopharma? CRISPR-Cas9 is probably the closest we get.

WHO WILL BE THE ELON MUSK OF BIOPHARMA?

Julia Owens, Ph.D.
Millendo Therapeutics

I don't believe there is an "Elon Musk" of biopharma, in large part because of the constraints of the industry itself. In biopharma, our discovery and development efforts usually happen outside of the limelight and over longer periods of time. We've seen breakthroughs in the past decades, including combinatorial chemistry, RNAi (RNA interference), and the sequencing of the human genome, which many predicted would fundamentally transform biopharma but have failed to dramatically alter overall timelines and costs of drug discovery and development. With those innovations have come some larger personalities, including Craig Venter (Celera) and John Maraganore (Alnylam). Other technological innovations are coming too, including more focused clinical studies — leveraging genetically directed, defined patient populations — which will drive efficiencies. But nothing appears likely to be so disruptive as to give anyone the mantle of "the Elon Musk of biotech." The late Henri Termeer is the closest we've come. But even he did not transcend biopharma.

HOW SHOULD BIOPHARMA PREPARE TO CAPITALIZE ON THE NOTION TOP TALENT, NOT CAPITAL, WILL DRIVE SUCCESS?

Sam Kulkarni, Ph.D.
CRISPR Therapeutics

Over the last 10 years we've seen that highly specialized and focused teams with the appropriate resources can be much more productive than large distributed R&D groups with siloed functional expertise. This phenomenon is seen also when comparing the productivity of small biotechs vs. the R&D organizations of large pharma companies on a normalized spend basis.

3 QUESTIONS FOR A BIOPHARMA BILLIONAIRE

In June 2011, Randal J. (R.J.) Kirk was first featured in *Life Science Leader*. At that time, he was a little-known serial entrepreneur who started, grew, and sold three biotech companies. He also was a billionaire. In the seven years since, he has nearly doubled his wealth while also starting another company, Intrexon (NYSE: XON), which has dazzled us with nonbrowning apples, cloned kittens, and genetically modified mosquitoes to fight the Zika virus. When invited to participate in our annual outlook issue, Kirk responded, "It would be my pleasure to participate. This will be fun." As usual, his insights do not disappoint.

HOW DO YOU ENVISION AI OR OTHER TECHNOLOGIES IMPACTING BIOPHARMA?

The impact of machine-learning capabilities on biopharma will be enormous. Due to its massive complexity, biology resisted engineering longer than almost any field of technical human endeavor. We simply did not know enough to engineer anything with reliability. Today, however, in many cases, we know enough to be able to engineer to a result within a calculable probability range, and this has led to a very large number and wide variety of "high throughput" R&D programs, with the intent that the throughput will compensate for the many uncertainties that remain latent within models. Machine-learning systems, on the other hand, work well with probabilistic models. Currently, massive machine-language processors and software programs are in development, and as these technologies become applied to biology, we shall see the perfect marriage of IT and biotechnology.

WHAT MACRO TREND WILL TAKE HOLD IN BIOPHARMA?

The shift from a discovery-based industry to one that engineers its new products has been ongoing for three decades in biopharma, so the latter now represents the dominant motif. While industry has been reasonably quick to adapt to the promise of these technologies in terms of driving to results more quickly and cheaply, few of the other implications seem to have been broadly grasped by industry constituents. For example, once new products become the result of engineering, maintaining a leadership position or a franchise position of any type will require a commitment to continually engineer the product and improve upon it constantly. The industry's former system of competing for monopolies of various types that reasonably could be expected to endure throughout the patent life of the initially approved product is, in my opinion, not likely to recur.

WHAT INNOVATIVE COMPANY OR PERSON OUTSIDE OF BIOPHARMA DO YOU PAY ATTENTION TO?

Facebook and Amazon illustrate different sides of how to perpetuate innovation in large companies. I enjoy watching Facebook for two reasons: First, they continue to reimagine what it means to lead the space they are in, successively upsizing the opportunity and then executing against the new challenge they just posed. Second, it is fun to watch them figure out how to manage their asset in the face of technophobia or some related public backlash. Whether the issue has been cyberbullying, fake news, or interference with elections and civil engagement, they seem initially to have been caught by surprise, but then quickly pivot to figure out how to manage their product responsibly in the face of the new challenge. Amazon, in some ways the opposite of Facebook, is always worth watching, because rather than working to expand and differentiate a single product, they develop lobes of capability and then seek to apply these to new space, sometimes with or without other internal lobes onboard. They seem always to have known, for example, that the cloud would happen as an infinitely scalable thing, and this would be a utility they not only could sell, but could utilize to enter and dominate diverse markets. With more lobes and markets comes a greater number of synergistic undertakings that become available. Imagine the number of arrows going every which way on their whiteboarding of the Whole Foods acquisition idea: By the time they were done, no doubt they had more arrows than boxes!

The primary relevance of these two companies to the biotechnology leadership is clear: We have been horrible at managing our product socially (unlike Facebook), and very few of our industry participants ever seriously consider what their real lobes of capability are, let alone search for ways to use them (unlike Amazon).

WHAT MACRO TREND WILL SOON TAKE HOLD IN BIOPHARMA?

Michelle Dipp, M.D., Ph.D.
Managing Director, General Atlantic
Former CEO of OvaScience

Mobility. While many of us travel internationally, some are preparing for their trip to Mars! While this is an exciting development, it also opens the door to a whole new universe of global health challenges that demand tech-enabled and innovative solutions to allow us to do everything from tracking/controlling epidemics, to storing vaccines, to enabling wellness in outer space.

WHAT METRICS DO YOU USE TO IDENTIFY KEY TRENDS?

David Meek
CEO of Ipsen

For me, the most significant is patient-centricity and, most importantly, the number of patients we treat with our medicines. As part of our overall growth strategy and to better address patient needs, we have set a target to launch a new drug or meaningful new indication for an existing drug every single year.

INSIGHTS FROM J&J'S CHAIRMAN OF THE BOARD AND CEO, ALEX GORSKY

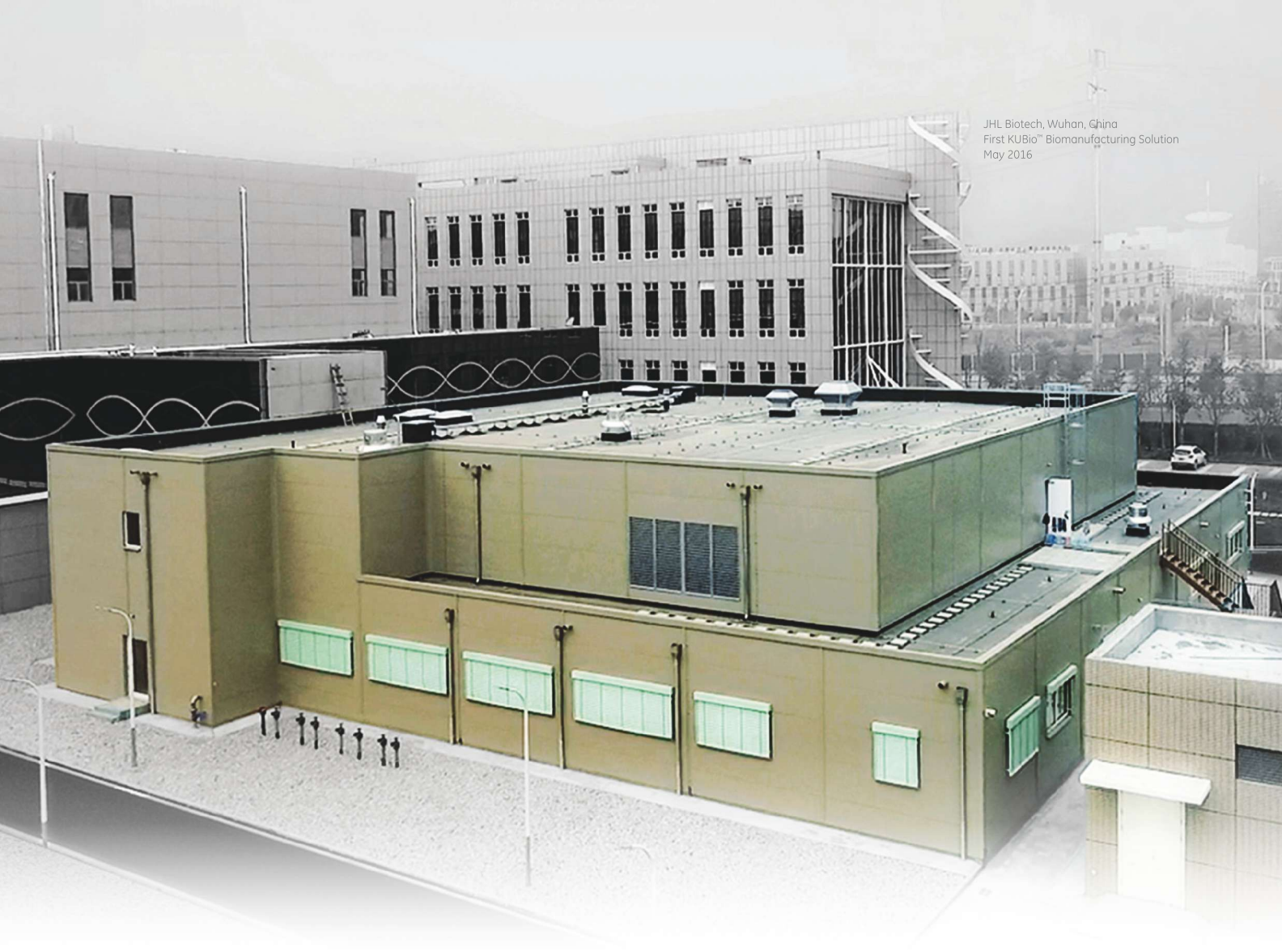
J&J's current CEO, Alex Gorsky, joined the company following six years of service in the U.S. Army. Having finished his military career with the rank of Captain, Gorsky began his career as a field sales representative with Janssen Pharmaceutica, and he is the only current top 10 Big Pharma CEO who can claim to "having carried a bag." What are some of the trends he is watching for in 2018?

GLOBAL HEALTHCARE TRENDS IMPACTING BIOPHARMA IN 2018

The digital information revolution is enabling unprecedented global collaboration and private-public partnerships to advance medicine and health and wellness. Collaboration drives innovation and will lead to more targeted, efficient, and earlier intervention. We will be able to intercept disease earlier and earlier, even before symptoms develop. We can expect effective vaccines for HIV, lung cancer, and Hepatitis B. We can easily imagine the elimination of Hep C and tuberculosis. We also will be creating effective new treatments for dementia and Alzheimer's disease. The opportunity for helping people live longer, healthier, and happier lives has never been greater.

GLOBAL MACRO TRENDS IMPACTING BIOPHARMA IN 2018

Despite improving economic conditions, governments will continue to be cost-conscious in confronting the global challenge of providing access to quality healthcare to more people, everywhere. That is particularly the case in healthcare in the U.S. We must move from a system that has, for a long time, emphasized paying for volume in care, to one that emphasizes paying for value. We must put the focus on the patients' needs first and on outcome for patients and their families — then define what achieves that best result. I am very optimistic for young people today. They are engaging in their health in new and different ways. Access to information on health and wellness, greater transparency on the part of the healthcare industry, and the continuing march of new technologies will allow them to be what I call "Generation H" — the healthiest generation in the history of humankind.



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THE WOMEN OF BIOPHARMA

WILL THEY GAIN OR LOSE GROUND IN 2018?

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

What were the wins and losses for women in the industry during the past year, and what is their outlook for the coming year? We wanted a real-time assessment from the people most affected by those questions — women executives. The advocacy group, Women In Bio, backed by LifeSci Advisors, helped us recruit leading women in biopharma companies and organizations to share their views of women's current state of progress and the prospects for short-term change in the industry.

In all, we hear from 11 women and one man in biopharma. Although we were not aiming for "balance" here — there are plenty of opposing opinions out there already — the sole gender-exception in this group supplies another valuable viewpoint, that of a man working hard to help other men see the world the way women in biopharma often see and encounter it.

This was not a survey or even a scientific sampling of opinions, however. We cast a wide net in numbers, size, and type of companies and organizations to seek input, but the main mission was to find women who would take the time and risk to write down deeper thoughts on the key issues. I say "risk" because one of the barriers for women appears to be the relatively high risk they face in individually declaring their views on controversial subjects. Risk may increase in proportion to size of company, perhaps explaining why almost all of our respondents lead startups or smaller pharmas. (See sidebar on right for a full list of respondents.)

Essentially, I have taken all the written responses and condensed them below with summaries and selected quotes. We will post a complete transcript of the full responses on our website in parallel with this print article.

Our panel members are all leaders in their companies or fields who contributed their thoughts on women in biopharma to this virtual roundtable discussion:

Faith Charles
Corporate Transactions & Securities Partner & Life Sciences Chair
Thompson Hine

Sue Dillon
Global Therapeutic Area Head, Immunology
Janssen

Karin Hamberg
SVP, Medical & Regulatory Science
Lundbeck

Britt Meelby Jensen
President and CEO
Zealand Pharma

Lee Jones
CEO
Rebiotix

Seema Kumar
VP, Innovation, Global Health, & Policy Communication
Johnson & Johnson

Lori Lyons-Williams
Chief Commercial Officer
Dermira

Leah Makley
President & CEO
ViewPoint Therapeutics

Nawal Ouzren
CEO
Sensorion

Amber Salzman
CEO
Adverum

Sally Susman
Executive VP, Corporate Affairs
Pfizer

Michael Rice
Founding Partner
LifeSci Advisors

MEASURES OF PROGRESS

One matter that must be clear from the beginning of this discussion — the position of women at the executive and board levels in biopharma is far from equal to men's. Moreover, real barriers still exist to making it more so. If it were otherwise, an evaluation of women's progress toward equality would make no sense. Because progress for industry women can only happen through a series of positive events, minus the setbacks, our discussion starts with concrete examples of both in the recent past, as well as expectations for the immediate future. Though our virtual-roundtable panelists agree on many of the facts, they differ more often on possible remedies for the slow progress, and even current retrogressive developments, they see.

What were the main wins and losses for women in the industry during the past year, and what is their outlook for the coming year?

"I see slow but steady progress toward more representation of women in positions of leadership in the industry," says **Leah Makley**, president and CEO of ViewPoint Therapeutics. Makley and several other panelists mention they were particularly encouraged by the appointment of Emma Walmsley as CEO of GlaxoSmithKline last April.

Sally Susman, executive VP of corporate affairs at Pfizer, focuses on significant advancements in recruiting, retaining, and raising women into leadership positions. "As leaders in science and innovation, we are uniquely positioned to cultivate a climate of science and engineering that encourages women to dive into these traditionally male-dominated fields." She points to Kirsten Lund-Jurgensen, who became the executive VP and president of Pfizer Global Supply. "Kirsten is the first woman to hold this position — it's exciting."

Though also seeing progress, **Lori Lyons-Williams**, chief commercial officer at Dermira, stresses the real facts in the slowly changing status quo: "Although recent estimates indicate that women currently make up about 50 percent of the talent pool in biopharma and hold more than half of the doctorates, only 18 percent of the highest-valued biotechnology companies have women in senior and C-suite management positions." On the other hand, she too includes Walmsley's appointment among the "meaningful wins" for industry women in 2017.

Yet **Nawal Ouzren**, CEO of Sensorion, points out an awkward, controversial, and all-too-typical fact in the Walmsley story: "She is paid 25 percent less than her predecessor, but I can't imagine the GSK board lowering their performance expectations by 25 percent." Still Ouzren recognizes big exceptions to the rule of men, such as Kate Bingham, managing partner, SV Life Sciences in London. "Not only is she one of the most influential women in European biotech, she has been engaged with the issue of diversity in biotech. She was one of the writers of the open letter against having women as 'eye candy' in professional biotech events, which got major media coverage."

Sue Dillon, global therapeutic area head, immunology, Janssen, cites other "wins" for women, such as company leaders taking action against "gender discrimination and harmful gender stereotypes" and the push by Women In Bio and others to diversify company boards, where women are still "woefully underrepresented." Dillon lists several women executives who have made significant strides: Samantha Du, Ph.D., chairwoman and CEO of ZAI Lab in China for building a China and global portfolio; Anna Protopapas, CEO of Mersana, who led a successful IPO in 2017; and Katrine Bosley, CEO of Editas, for pioneering gene editing. On the other hand, she says current lawsuits to fight gender discrimination, such as by Vicki Lundblad and Katherine Jones at the Salk Institute, unfortunately recall Dr. Nancy Hopkins' seminal work in the 1990s, detailing discrim-

ination against women at MIT. "It's depressing to hear about similar issues in 2017."

On the subject of recent setbacks, **Lee Jones**, CEO of Rebiotix, points to a discomforting example: the spectacular downfall of Elizabeth Holmes of Theranos. "Her rise and fall has been mimicked many times by several men, but her story stood out for me because she was female. Unfortunately, it will stand as an example, probably until the end of time, of why not to invest in a woman-led company." In contrast, when women move up in responsibilities, start companies, or accomplish great things, Jones sees noticeably less press coverage than for men when they do the same.

Part of the problem may be the disparity in numbers, leading many among the press and industry leaders to form a lazy habit of ignoring the achievements of women. "The big loss must be that there are still far too few female senior executives," says **Britt Meelby Jensen**, CEO of Zealand Pharma. "The picture is slightly better when it comes to female representation at board level, but it remains critical to improve female representation at the executive level, as this is the food chain for future qualified board members."

Adverum CEO **Amber Salzman** says her company "actively recruited top talent, and it happened to be that the most talented candidate for Chief Medical Officer was a woman — Athena Countouriotis." The executive team is 80 percent female, creating "a top work environment that has already paid off." A recent hire said he joined Adverum because of the work environment and leadership at the top. "We have a very collaborative environment, and the diversity of thought has enabled us to problem-solve difficult challenges." Salzman is heartened by the rise of shareholder pressure on companies to diversify their boards: "There are some extremely talented women who could significantly enhance a board but are not yet on the radar as their male counterparts are."

Confirming the disparity, **Michael Rice** of LifeSci Advisors, cites research published this year by MassBio and LiftStream that documents the slow progress toward gender diversity in the industry. At the present rate, LiftStream predicts it will take the industry 40 years to reach parity at the board level. "That's not nearly fast enough," he says. "We still have a lot of work to do, and men need to be allies in this work. The more people we have aware of and actively engaged in making change on this issue, the faster we're going to effect positive change in our industry."

Faith Charles of Thompson Hine emphasizes the potential benefits of speeding up progress. "Creating and fostering a diverse and inclusive corporate culture strengthens any organization. Having women at the C-level, in the boardroom, or as outside counsel advising a company's officers and board members adds a perspective that may not otherwise be present." She commends leading companies, such as Biogen and J&J, for developing best practices in hiring and other areas affecting, and affected by, gender diversity.

A more international perspective comes from **Karin Hamberg**, who heads medical and regulatory at the Danish company Lundbeck. Despite the continuing imbalance and slow progress, she acknowledges, "Gender diversity is increasing in importance as a driver of the business, and many multinational companies are now investing billions of dollars in diversity initiatives."

Seema Kumar, VP of innovation, global health, and policy communication at Johnson & Johnson, puts a bookend on this part of the discussion with signs of progress: "One win worth celebrating is that in 2017, the number of women CEOs running Fortune 500 companies reached an all-time high. These 32 women mark the highest population of female CEOs in the 63-year history of the Fortune 500. That said, of course, we women executives would like to see the numbers climb up much higher. Our challenge for 2018 is to elevate women of all backgrounds and ethnicities into executive positions."

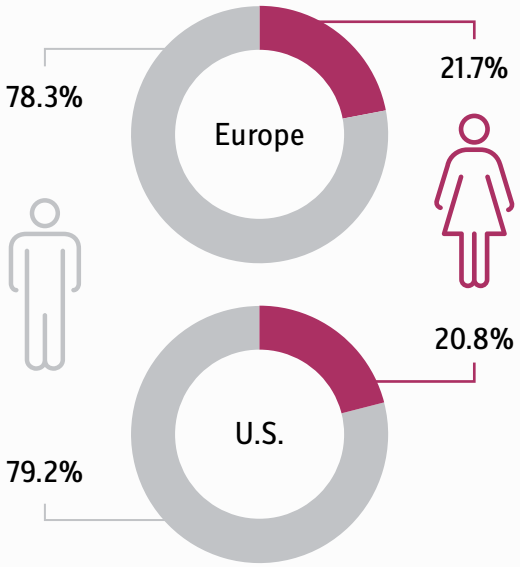
WALLS OF ASYMMETRY

Is it the same world of opportunity for the men and women of biopharma? Our panelists answer with a unanimous and emphatic no, even if some of them have fortunately avoided the worst barriers for women in their own careers. One perception they all share is of the "unconscious bias" that works to perpetuate itself in an industry still mainly under male control. The relevant statistics show how real the control is. (See "Women Make Up ..." and "Gender Diversity ..." on page 21.) Here, the panel members deliver a dispassionate yet overpowering plea for the industry to pay conscious attention to the unconscious habits retarding progress for the women of biopharma.

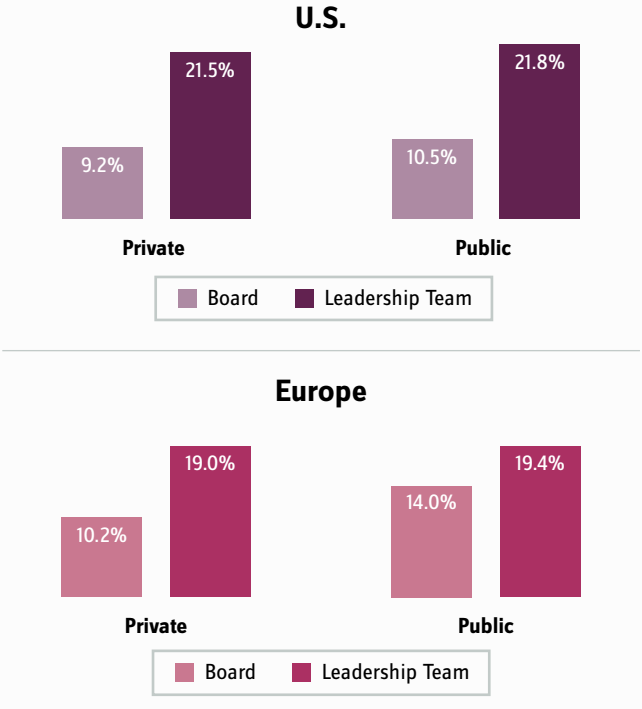
What are some of the common obstacles women executives in the industry still face that men commonly do not?

Salzman succinctly states a shared observation: "I still see more unconscious biases and different assumptions being made about women than about men. It's human nature for people to relate more to people who are 'more like themselves' and who have grown up with 'similar' experiences. Being a different gender makes you less similar."

WOMEN MAKE UP LESS THAN 25% OF LEADERSHIP TEAMS



GENDER DIVERSITY DOES NOT INCREASE FOLLOWING PUBLIC LISTING



SOURCE: "Diversifying The Outlook: The X&Y Of Biotechnology Leadership" – Liftstream

"Janssen and Johnson & Johnson have an inclusive culture, and I've not experienced obstacles during my tenure — in fact quite the opposite!" says **Dillon**. She observes, however, that all women in business have likely had the experience of being the sole female in business meetings or functions "where it was a struggle to truly have a seat at the table."

Meelby Jensen elaborates: "Women often have to more consciously engage in a 'relatable' way and find styles of communication that reinforce their ability to be 'heard' by men to operate and deliver for their businesses." She faults inadequate attention to recruitment and promotion of C-level women executives, reflecting a widespread but unconscious gender bias and the traditional camaraderie of men. "Overall, I think men are better at networking and promoting themselves and each other than women, and they are less reluctant to take risk. Some women could push themselves more to jump into unknown territory, be better at helping each other to succeed, while also getting into the game of networking."

Enumerating the most typical challenges for women, **Ouzren** lists conflicts with raising a family, lack of available female candidates for very senior roles, data demonstrating that female CEOs have more challenges to raise money than their male peers, and a "Boy's Club" corporate culture that sees no reason to support diversity and limits senior-leadership support, mentoring, and sponsorship of female executives.

Hamberg cites a specific family-related challenge, when women must take maternity leave or time off to attend to small children early in their careers — permanently lowering their salary levels and benefits. Although she sees no easy solutions, she considers practical ways the industry could approach the imbalance. In some Scandinavian countries, she notes, such leaves are granted only if the father joins the mother in the time away from work. "Generally, I believe people should be rewarded based on their business contribution, not based on seniority or 'fairness' principles," she says.

"Women still report feeling more pressure to choose family versus advancing their careers compared to men and often don't receive access to the supportive programs they may need to help them succeed," says **Lyons-Williams**. Despite many women building careers in the life sciences industry, she notes there are still fewer women entering and graduating with science and technical degrees, compared to men. "When women do elect for a career in life sciences, two of the more common obstacles I've seen are related to compensation and career development. On average, women are paid less and lack the same career trajectory with regard to promotions and advancements as their male colleagues." She is concerned the repeating cycle of lowered expectations may keep industry women in

a permanent minority at the top levels. "Younger women often assume that if they don't see women in leadership, the personal and professional obstacles will be too large for them to overcome."

Seeing generally high regard for diversity and support for women at Pfizer and industrywide, **Susman** also recognizes persistent "unconscious biases" in the biopharma sector. "This is challenging to address because these are the unfounded stereotypes that people form outside of their own awareness," she says. In business, she has witnessed male aspirants given the benefit of the doubt when presented with a promotion or increased responsibilities, yet women needing to prove themselves before, during, and after the offer has been extended. "We need to reach a time where an established, professional woman can walk into her corner office without feeling she has to validate her reason for being there."

"We can blaze our own trails," adds **Kumar**. "Although we have come quite far since the days where women had to act like men to be taken seriously, I believe that female executives still have a higher hurdle and find themselves working harder to prove their value." Like the others, she points to "hidden, and sometimes unconscious, biases" facing women in the industry and showing the need for further progress.

Jones is unequivocal in her observations of continuing barriers for women in biopharma as a self-perpetuating problem. "It is difficult for women to gain professional recognition when they remain outside the long-established network for men," she says. "I see lots of money being thrown at male executives who start their own companies or move to a startup company because someone else, generally another male, sees them as being smart. Women are held to a much higher standard." Men, most often the ones hiring and recruiting, often cite lack of qualified women candidates. "What they mean is that they didn't find them in their networks."

"It all comes down to earning respect, being seen as having the same qualifications and skills as our male counterparts, and being given the same opportunities they receive," says **Charles**. "We're making progress here, too, but old ideas and old habits die hard; it takes time to overcome long-held beliefs and stereotypes." She believes women could make much more use of mentors and sponsors. "Women often tend to be more passive and think that having education, exceptional talent, and proven experience will get them where they want to go, but as the old adage goes, it's not what you know, it's who you know."

Rice has witnessed the barriers for women from a man's perspective, and the experience has motivated him and his group to support Women In Bio's Boardroom Ready program. "Many boards and leadership teams are looking for people with prior board experience — but this creates a cycle of keeping women off boards because, without being on a board, you can't gain the experience required to be on one," he says. He believes the male-dominated boards gravitate toward staying with the familiar status quo, rather than making positive efforts to bring in women and mentor them in the art and politics of board management.

FASTER MOTION

Our panelists explore how the right actions taken now could accelerate the pace of change for the women of biopharma, by tackling the following question.

What should be the specific, immediate steps in furthering industry women's progress in 2018?

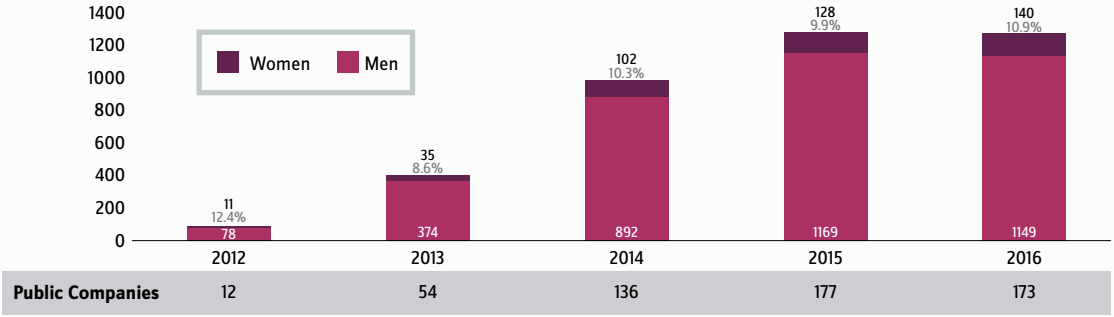
Kumar opens this phase of the discussion appropriately — with a call to action: "Women, and particularly minority women, need to express their voice, and act as role models to pave the way for future generations of diverse leaders in the biopharma world," she says. "Storytelling plays a tremendous role in furthering progress for women. Positive role models allow women to not only dream of being successful in the industry, but seeing that these achievements are possible." As part of "doing her part," Kumar has been publishing a Women in STEM LinkedIn series, highlighting the female heroes of STEM, both past and present.

A much larger group of women than represented here, who now run companies and organizations all over the industry, also have considerable power to move history forward for women. "In my company, I will continue to focus on building the best product and company I possibly can," **Makley** says. "I hope that, in doing so, I also will help shift the entrenched pattern and make the path a bit easier for the next female founders who come along."

Quite a number of our panelists also had firm views of what actions companies should take and what standards they should follow in changing the diversity scales. "Companies should take on measurable diversity goals from entry-level positions all the way up to their boards," says **Salzman**. "That's the only way to move past the unconscious biases that often take place."

According to **Lyons-Williams**, only one woman currently serves on her company's board, and Lyons-Williams is the only woman in the C-suite. She sees an opportunity for these numbers to improve over time, since

NUMBER OF BOARD DIRECTORS IN NEW PUBLIC-LISTED BIOTECHS



Public Companies	12	54	136	177	173

more than 60 percent of her company's employees, including seven VP-level functional leaders, are women. "There are talented women who are capable of rising to the ranks of the C-suite or board. It is our duty, as executive leaders, both men and women, to do more than mentor these individuals. We must actively identify development opportunities and pave career paths for these women."

Jones adds more detail to the action agenda: "Every hiring manager in biopharma should be challenged to interview as many women as men for every job and should be encouraged to hire as many women as they do men for the jobs they have open. It may surprise people that qualified women are indeed available if one looks. The result of that will be to create a culture where people are valued for what they bring to the table, and the companies will be better able to serve their customers."

Drilling down further, **Ouzren** would score the game: "I would start working on the metrics and set up targets to close the gaps, ASAP, in board representation, salary, and percent of diversity in the workforce. Every CEO should hold their direct reports accountable to close the gaps — and it should be part of year-end performance feedback and subsequent salary increase or equity payoff. One quick win is to make sure that you have a diverse pool of candidates for every single position and, in particular, very senior ones." If industrywide progress still lags, Ouzren believes policymakers should take charge; Sweden mandates a 50/50 men/women representation on boards for private and public companies.

Hamberg's faith in such efforts is limited: "Personally, while I acknowledge the value of general diversity, I am not a big fan of policies favoring more women in business. Long term, I believe the best way to achieve equality is to ensure women have the qualifications and support they need to be successful in the workforce. One key way to achieve greater equality of opportunity in the workplace is to provide free education as the Danish government does. Free access to higher education for everyone is critical to developing a strong talent pool and is an immensely important factor for securing diversity." She believes more-immediate drivers of change would be increased adoption of flexible working conditions, talent development, and mentorship programs.

Merely hiring more women in the industry is not the answer, says **Charles**: "We must first understand the underlying causes to find solutions. We need to continuously analyze whether plans we put in place are working and whether our initiatives and organizations are making progress, not just form a committee so we can say we have one. Committees and initiatives charged with implementing changes to create and sustain diversity must be empowered and given the resources to actually make a difference. Above all, women need to have more confidence in themselves and take control of their careers. Enlist a sponsor, network, let people know you are looking for CEO or other C-suite jobs, and pursue your desires fearlessly."

"Everyone needs to get involved in this issue if we're really going to effect change across the industry and make it a more inclusive space. We need to keep having open, honest dialogues and really listen to women in the industry, and then we need to take action," **Rice** says.

Building women's presence on boards and in executive roles is essential, and progress is happening — but not fast enough, **Dillon** believes. Beyond the growing network of female executives, and male supporters, she sees promise in training and mentoring the next generation of women to unleash their potential and personal confidence early in their careers. "I'm optimistic that this tsunami of next-generation talent, connected with the growing cadre of established women leaders, will break barriers like we've never seen."

"We have four strong female leaders on Pfizer's executive team, and I feel incredibly fortunate to be one of them," says **Susman**. "Based on my experience, I feel the paradigm shift for Pfizer is well underway — we're excited about where we're headed, and we're going to continue this momentum forward through 2018 and beyond."

Meelby Jensen seems to sum up a lot of our panel's views in these few words: "Many mistake the issue of gender diversity as being for women alone. Both men and women are needed to enable change, and we need to look beyond gender bias to capture the very best leadership talent. I encourage women to go for the opportunity and also urge that they are given the opportunity to prove that they can do the job. I guarantee that we can!" L

Are You Ready For The Future Of Biopharma Manufacturing?

ROB WRIGHT Chief Editor @RfwrightLSL

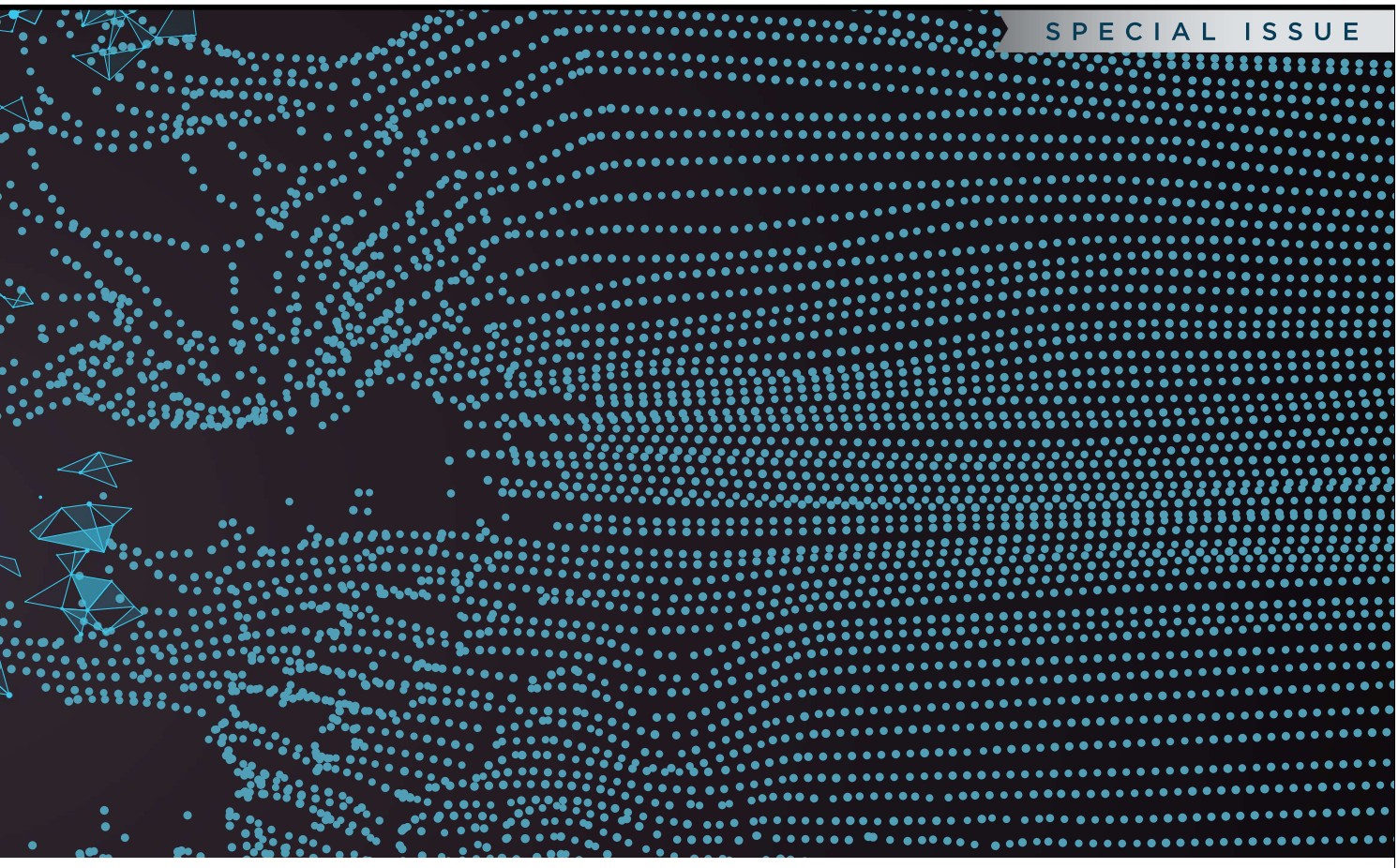
In last's year's manufacturing outlook we delved into biopharma's manufacturing capacity crunch. While lack of manufacturing capacity remains a challenge for the industry, the future of biopharma manufacturing has never looked so bright, and there is a variety of reasons why. For starters, when it comes to innovation in manufacturing, biopharma companies continue to push the envelope. Want proof? Take a quick review of the ISPE Facility of the Year Awards (FOYA), an annual program recognizing state-of-the-art projects by biopharma manufacturers. There you'll see some old standbys (e.g., Abbott, Bristol-Myers Squibb, and Lilly) being recognized for operational excellence (OPEX), facility integration, and process innovation, but you'll also encounter some lesser-known names. For example, Kalbio Global Medika's young team (average age of 24) received an honorable mention for its 40,000-square-foot biotechnology manufacturing build in Jakarta, Indonesia. Nephron Pharmaceuticals Corp., another honorable mention, is a woman-owned business that also happens to be the world's largest blow-fill-seal manufacturer.

Another reason for optimism is the volume of incredible technological innovations beginning to make their way into biopharma manufacturing operations. Beyond those technologies, though, is the talent that will ensure proper implementation. With that in mind, for this year's manufacturing outlook we assembled the biggest and most diverse group of biopharma manufacturing thought leaders *ever*. You'll hear from Big Pharma, virtual biopharma, and U.S. regulatory leadership, as well as international perspectives, for what to expect in biopharma manufacturing for 2018 — and beyond. So let's begin.

WHAT INNOVATIVE SOLUTIONS TO THE CURRENT BIOPHARMA INDUSTRY MANUFACTURING CAPACITY CRUNCH NEED TO BE IMPLEMENTED TO MEDIATE THE PROBLEM?

Paul McKenzie, Ph.D.
EVP Pharmaceutical Operations & Technology
Biogen

As the pipelines of innovators continue to diversify across modalities, every company will face the challenge of building needed capabilities for all modalities, while maintaining existing capacities and capabilities consumed by the current portfolio. In addition to this diversification, the productivity of more mature modality platforms is increasing significantly, driving current facilities to be underutilized or in need of redesign. This inflection point will create the need for different partnership models amongst innovator companies, as well as between innovator companies, CMOs, and laboratory organizations. Since owning everything will be a signif-



icant financial burden, the onus will be on each company to clearly delineate what it can manage and access through these partnerships.

WHAT DISRUPTIVE TECHNOLOGIES WILL TRANSFORM BIOPHARMA MANUFACTURING IN THE NEXT THREE TO FIVE YEARS?

Wolfram Carius, Ph.D.
Head of Pharmaceuticals
Product Supply
Bayer

Gene and cell therapy seem to be at the edge of having a transformative impact on different therapeutic areas such as oncology, immunology, or hematology. This will intensify beyond the five-year horizon as advanced technologies like CRISPR-Cas9 or viral vectors will accelerate innovation tailored to patients. This too, will significantly transform the value chain and operating model in the market within the biopharma industry. Drug-device combinations, be they for diagnostics, IT support (e.g. monitoring compliance), or drug application, also will increase, making an end-to-end setup of our organizations ever more important. At the same time, both improvements and step changes through advanced analytics and artificial intelligence (AI) also will reach the pharmaceutical sector, not just in clinical development but probably also initially in supply chain and quality and then in technical development and manufacturing. Big Data managed along the entire supply chain will provide real-time transparency, and many supply chain process steps could be performed by self-learning computer systems. Robotics and evolution toward real-time controls through advanced analytics will further improve cGMP compliance and product quality by speeding up process robustness and quality control, thus also accelerating technical development and manufacturing, which will be on a steady, critical path for new product launches.

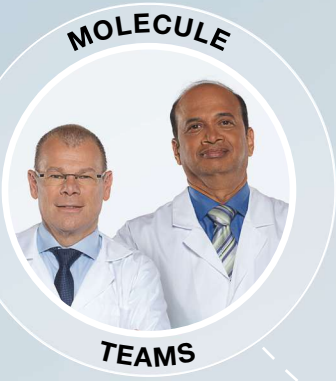
WHAT BIOPHARMA MANUFACTURING TRENDS DO YOU FIND MOST EXCITING?

Roger Connor
President Global
Manufacturing & Supply
GSK

When we couple modular design with continuous manufacturing, then we can truly create a flexible pharmaceutical manufacturing space that is genuinely transformative. The footprint and equipment scale of these modular-design continuous plants will be completely different from what we know today and will enable significant reduction in operating costs while virtually

The People and Science Behind

Patheon OneSource™ for Small & Emerging Pharma



2400+ scientists ready for your challenge

The Drug Substance Molecule Team collaborates with the Drug Product Team to ensure that your molecule becomes a formulation-ready API. The integrated Molecule Team is a key driver of the Patheon OneSource™ time savings.

Andreas Stolle, Ph.D., joined us in 2015
Vice President, API Process Development Services

560+ development programs in 2016

Whether you are working with a large molecule or a small molecule, your Drug Substance Project Manager proactively works to ensure your molecule has its best shot at success by maintaining timelines and minimizing potential rework during development.

Angela Colarusso, joined us in 2007
Sr. Director, Biologics Program and Proposals Management

Smart sourcing
Procurement experts assist with sourcing generic API and raw materials to ensure availability and reliable supply.

Simplified administration
If it works better for your business, we can establish one Master Service Agreement, one Drug Substance/Drug Product Contract and one Quality Agreement. This also means one taxation and regulatory structure, one currency and one invoicing process.

Faster Drug Development

We develop 75% of all dosage forms

For large and small molecules, close collaboration with the Drug Substance Molecule Team allows the application of right-fit science for formulation, process development, tech transfer and scale-up to ensure a smoother transition to market.

Anil Kane, Ph.D., MBA, joined us in 2000
Executive Director, Global Head of Technical & Scientific Affairs

CLINICAL TRIAL MANUFACTURING

112 NDA approvals in 10 years

More than 2x any other CDMO

For both large and small molecules, the Patheon OneSource™ methodology minimizes failures due to foreseeable events and maximizes your molecule's chances of out-licensing or making it to market.

DRUG PRODUCT PROJECT MANAGER

Stability and scalability

By collaborating with the Drug Substance Project Manager, the Drug Product Project Manager ensures your trial-level drug product is also suitable for scale-up.

Nicky Arvanitis, MBA, joined us in 1997
Director, PDS Project Management

CLINICAL PACKAGING AND DISTRIBUTION

Securely packaged for on-time distribution

Combining best-in-class robust primary and secondary clinical packaging and secure on-time distribution to meet quality standards and patient compliance.

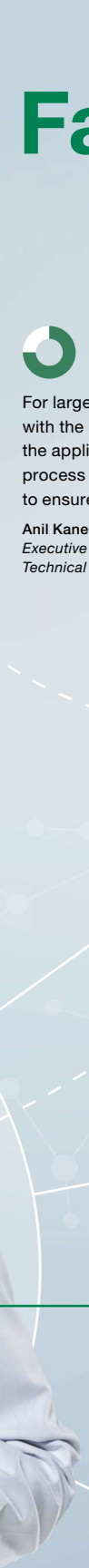
BACK-UP PROGRAM MANAGER

We always have a back-up plan

To ensure your molecule never goes off track, every team includes a Back-up Program Manager ready to step in any time life gets in the way.

Save an average of 14 Weeks & $44.7M[1]

Something needs to be done about the high cost of drug development. By combining drug substance, drug product, clinical manufacturing and clinical packaging into a single process, Patheon OneSource™ accelerates your molecule like nobody else can.



Speed through communication

The Program Manager is the architect of your drug development program. This single point of contact both within Patheon, and with you, simplifies every interaction and manages your molecule's critical path to deliver unmatched time and cost savings.

Aaron Williams, PMP, joined us in 2011
Program Manager, Patheon OneSource™

Patheon part of Thermo Fisher Scientific | OneSource™

www.patheon.com/onesource

1. Assessing the Financial Benefits of Faster Development Times: The Case of Single-Source vs. Multi-Vendor Outsourced Manufacturing, Tufts Center for the Study of Drug Development, 2017

JANET WOODCOCK ADDRESSES BIOPHARMA MANUFACTURING'S FUTURE

As the Director for the CDER and an FDA employee since 1986, Janet Woodcock, M.D., holds a special place in the world of biopharma manufacturing. Under her leadership, we have witnessed the introduction of risk management as a new approach to drug safety, the "Critical Path" Initiative to move medical discoveries from the laboratory to consumers more efficiently, and the "Pharmaceutical Quality for the 21st Century Initiative," the FDA's highly successful effort to modernize drug manufacturing and its regulation. Here is Dr. Woodcock's biopharma manufacturing outlook for 2018 – and beyond.

WHAT DISRUPTIVE TECHNOLOGIES WILL TRANSFORM BIOPHARMA INDUSTRY MANUFACTURING IN THE NEXT THREE TO FIVE YEARS?

We will continue to see the adoption of continuous manufacturing technologies. These technologies may soon begin to integrate drug substance and drug product manufacturing in the small molecule space and upstream and downstream processing in the biological product space. This should be a positive trend as it can potentially enable higher product quality, lower manufacturing costs, smaller facility footprints, and improved agility. Coupled with this, we also may see advancements in process analytical technology (PAT) and model-based control strategies enabling real-time monitoring of product quality at unprecedented frequencies and real-time product release decisions without end product testing. Also on the horizon are new dosage forms enabled by additive and other manufacturing technologies that can accommodate specialized patient needs. For example, this might include easy-to-swallow drugs or drugs with specific release rates. These technologies may even be mobile or on-demand. These smaller manufacturing platforms may enable on-site drug manufacturing at pharmacies, hospitals, or sites of public health emergencies. The rise of digital medicine also could allow us to more closely link drug quality to individual patient impact than ever before.

WHAT IS YOUR VISION FOR HOW THE GLOBAL BIOPHARMA MANUFACTURING INDUSTRY COULD LOOK IN 2028 AND BEYOND?

Currently, the pharmaceutical manufacturing industry is still entering the stage of automation, while other industries are entering the stage of cyber-physical systems or Industry 4.0. Some in the FDA recently described a future vision of pharmaceutical quality and a potential path to get there. That future is Six Sigma pharmaceutical quality (i.e., no more than 3.4 defects per million opportunities). A path to get there includes economic drivers, performance-based regulation, Quality by Design (QbD), advanced manufacturing technologies, and continuous improvement and operational excellence (OPEX). To realize this future there need to be economic factors that recognize and incentivize quality. The regulatory approach must shift from predominantly management-based regulation to performance-based in order to give industry the necessary flexibility to improve quality. The adoption of emerging manufacturing technologies, including continuous manufacturing and advanced PAT, can enable higher quality. The knowledge gained from a QbD approach forms the basis for establishing a control strategy for these technologies. Finally, continuous improvement, OPEX, and a culture of quality must be part of the overall effort to drive quality in an organization. It is not unreasonable to think that the pharmaceutical manufacturing industry could follow this path to Six Sigma quality over the next decade.

WHAT ARE YOU DOING THAT WILL HAVE A BIG IMPACT ON YOUR MANUFACTURING ORGANIZATION IN 2018 AND BEYOND?

The CDER has an Emerging Technology Program to promote early engagement with firms to discuss potential challenges in implementing innovative approaches to pharmaceutical product design and manufacturing. We recently issued a final guidance for industry, "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization," with recommendations for firms that are interested in discussing these emerging technologies with the FDA. We recognize that adopting innovative approaches can present technical and regulatory challenges, including concerns about delays in the regulatory assessment process. With early engagement, the FDA can move more quickly to assess and act on applications involving new technologies. Along with this initiative, we have made an effort to provide staff with the knowledge necessary to handle such applications. Much of this knowledge stems from our research in both PAT and manufacturing science, which provides learning opportunities for our staff involved in application assessment. We've also taken steps to more fully integrate the human drug-assessment programs with facility evaluations and inspections. This enables better alignment between our field professionals and the staff who evaluate the products manufactured in the inspected facilities. The Emerging Technology Program could have a big impact on manufacturers in 2018 and beyond due to the potential for early face-to-face meetings even before identifying a lead drug molecule. These interactions then continue to provide regulatory feedback and facilitate the preparation of a regulatory submission.

"WHEN WE COUPLE MODULAR DESIGN WITH CONTINUOUS MANUFACTURING, THEN WE CAN TRULY CREATE A FLEXIBLE PHARMACEUTICAL MANUFACTURING SPACE THAT IS GENUINELY TRANSFORMATIVE."

Roger Connor
President Global Manufacturing & Supply, GSK

eliminating plant changeover time loss and freeing up capacity. Our networks will become far more flexible, and construction costs will decrease. Within the next 10 years, we could even see portable manufacturing facilities.

The opportunities for continuous processing in API manufacturing are particularly interesting and should provide far more robust and reproducible manufacturing platforms with significant scope for automation. Coupled with online analysis, which can shorten batch release times and improve data integrity, continuous processing will significantly reduce processing time.

WHAT MANUFACTURING TRENDS FROM OTHER INDUSTRIES WILL BEGIN TO SPILL OVER INTO BIOPHARMA IN 2018 AND BEYOND?

Robert Stewart
EVP, COO
Allergan

Pharma is still behind many other industries regarding investments in technology involving how businesses are run, compared with how products are made. We see the potential for continued investment and improvement here, learning from the fast-moving consumer goods and electronics industries which have demonstrated a proclivity for using much of today's innovation (e.g., cloud computing and the Internet of Things) to increase visibility to data and other trends to facilitate fast and more agile decision making across supply chains.

WHAT ARE THE TOP EMERGING INNOVATIONS THAT WILL IMPACT BIOPHARMA MANUFACTURING WITHIN THE NEXT FIVE YEARS?

Luscan Philippe
EVP Global Industrial Affairs
Sanofi

Certainly the way data can be exploited through cloud computing and the Industrial Internet of Things, for example, to enhance more effective and quicker decision making is a definite benefit. However, there is a perception that the biopharma industry has been behind the times in adopting some new approaches, but we should bear in mind that these emerging innovations come with unique risks that need to be managed carefully. For example, despite the obvious benefits of cloud computing, particularly in clinical research, it is imperative we keep any patient-sensitive data secure. How much risk a company is willing to take in this respect is likely to vary from one organization to another. While we should always proceed in new ways of working with necessary caution, it is certainly an exciting time to be involved in biopharma manufacturing, as ultimately all of these technologies will feed on one another as they mature.

WHAT IS YOUR VISION FOR HOW THE GLOBAL BIOPHARMA MANUFACTURING INDUSTRY COULD LOOK IN 2028 AND BEYOND?

Chun Zhang, Ph.D.
Head of Process Development
& Manufacturing
Evelo Biosciences

The industry will consist of several segments tailored to product platforms such as proteins, cell therapies, and gene therapies. They also will consist of different scales to meet the diverse product needs, ranging from blockbuster to individualized medicine. Large manufacturing plants are more cost-effective for commodity-type products, while smaller modular facilities will be tailored for niche products. Continuous manufacturing will be widely adopted and greatly enhance productivity and product quality, and true integration of information and data will enable rapid analysis and fast decision making. There will be much closer collaboration between manufacturers and suppliers in precompetitive consortia to drive standardization and automation, and as a result, supply chains will be more integrated and efficient in reducing inventory hold.

INSIGHTS FROM A BIOPHARMA MANUFACTURING TRAILBLAZER

Across races, females are earning more undergraduate degrees than their male counterparts, including disciplines of science and engineering. Why then are 38 percent of female engineers opting to leave their field? According to a national study, 30 percent of respondents cited an organizational climate characterized by nonsupportive supervisors or co-workers and general incivility, while nearly half left due to working conditions. So despite there being more women in biopharma manufacturing leadership roles, there aren't as many as there should be. This issue isn't related to female self-confidence or leaving the workforce for motherhood; it's a field that lacks a strong network of female leaders, necessitating aspiring women to have to blaze their own trail.

Chhaya Shah, one of two women trailblazers to participate in this year's manufacturing outlook, has had to overcome her share of adversity. For example, when she moved to the United States from India at the age of eight, she did not speak any English. Yet Shah went on to graduate from high school with honors. In her graduating class of over 3,000 students at Wilkes University, there were only three women (including her) in the college's engineering program. Shah has spent 19 years in biopharma manufacturing with the likes of Becton Dickenson, Abbott, Wyeth, and Shire, before taking on her current role as SVP of manufacturing and technical operations at Synergy Pharmaceuticals (NASDAQ: SGYP). Her perspectives are as diverse as her experiences – and they *do not* include a mention of the need for more women in biopharma leadership.

IS THERE A CURRENT BIOPHARMA MANUFACTURING TREND THAT HAS BEGUN TO DIE?

The traditional hierarchical organizational structure is not likely to last much longer. More companies are moving toward a team-based organizational structure. Top-down hierarchical organizations were originally designed for accountability. However, for successful organizations to compete and win in today's global market, they must be designed for speed, agility, and adaptability. As organizations make the transition to a team-based approach, they find smaller teams (i.e., five to seven people) to be a more natural way for employees to work. Whatever a hierarchical organizational chart says, real, day-to-day work is done in networks. Therefore, the organization of the future is a network of teams that are accountable for results and given the freedom to drive the required decision making to achieve them. Top-performing companies are built on systems that encourage teams and individuals to meet each other, share information transparently, and move from team-to-team depending on issues to be addressed. Different networks may have different specialties, such as innovation or getting a product to market quickly, but the principle is the same. Launching a product is a great example of where you need a team that is agile, networked, effective, efficient, and sharing a common goal. New organizational models also will require new approaches to leadership, and leaders of a team-based approach will need skills in the area of talent development, negotiation, resilience, and system thinking.

WHAT REGION OTHER THAN THE U.S. WILL HAVE THE BIGGEST IMPACT ON BIOPHARMA MANUFACTURING IN THE NEXT THREE TO FIVE YEARS?

Brazil, Russia, India, and China (BRIC) will likely continue to have a significant impact on biopharma manufacturing over the next several years. As the pharma market has flattened in the U.S. and many EU countries, the BRIC market has thrived due to improved standards of living, more citizens with access to health coverage, and an increased need for medicines related to noncommunicable diseases (e.g., diabetes, cancer, and cardiovascular problems). Pharmaceutical sales have doubled in these markets over the last five years, and projections show continued growth through 2020. Additionally, BRIC nations are looking at biosimilars as their chance to compete for a bigger chunk of the global pharmaceutical market. Many pharma companies have moved manufacturing locally or have partnered with companies in BRIC nations to improve access for their products, while also achieving more cost-effective and efficient supply. This has posed some challenges to industry, as GMP manufacturing expertise and the infrastructure in these markets have struggled to keep pace with the high demand. The companies that are most successful in meeting these challenges will reap the biggest rewards.

WHAT NONBIOPHARMA MANUFACTURERS WILL HAVE THE BIGGEST IMPACT ON THE INDUSTRY'S MANUFACTURING IN THE NEXT THREE TO FIVE YEARS?

Those working in the areas of artificial intelligence (AI) and robot manufacturing will have the biggest impact. This trend has been growing and will become more prevalent as biopharma manufacturers eventually have most of their tasks conducted through automated systems (i.e., even more than we do currently). Robots will conduct testing on production lines, enter results, and even conduct dual-quality checks. This trend already has been used in various other industries (e.g., automotive and electronics), and the cost savings are significant. Pharmaceutical companies will likely follow this trend and invest more in automation and robots and, in turn, move their human capital toward innovation vs. manufacturing. The advantages of complete robot manufacturing are evident: Errors are reduced, contamination limited, and overall assurance of a repetitious manufacturing process becomes more reliable.

WHAT'S GOING TO BE BIG IN BIOPHARMA MANUFACTURING IN 2018?

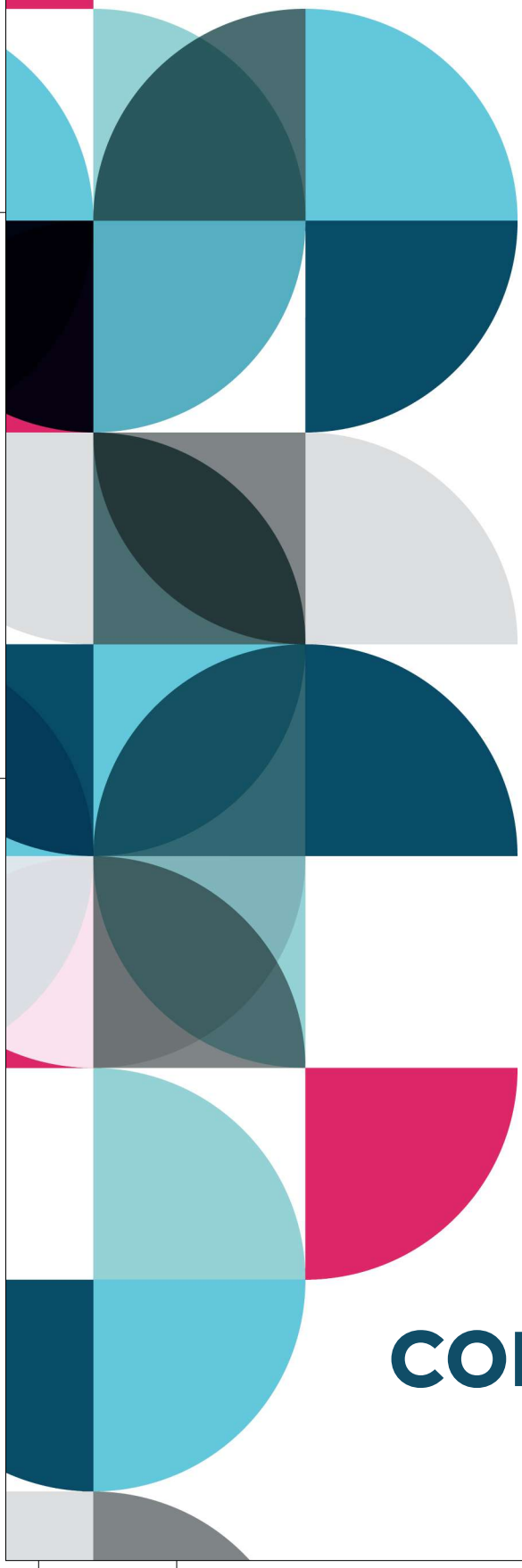
Esteban Santos
EVP Operations
Amgen

Clearly, the impact of Hurricane Maria on Puerto Rico and the importance of risk-mitigation and business-continuity strategies will be a topic of discussion in the biopharma industry well into 2018. After an event of this magnitude, the relevance of having well-rehearsed crisis-management and business-continuity plans rises to the top of everyone's list. Hurricane Maria tested the resilience of our industry's global supply chain, and from the lessons learned, industry needs to consider what improvements are to be made.

WHAT ARE YOU DOING THAT WILL HAVE A BIG IMPACT ON YOUR MANUFACTURING ORGANIZATION IN 2018 AND BEYOND?

Michael Thien
SVP & Head
Biologics & Sterile
Operating Unit
Merck

Investing in the infrastructure necessary to explore new processing and analytical technologies is a top priority. In order to define the technology/process of the future, investment is needed now to determine the selection of "intensification strategy." Factors being considered include existing manufacturing capacity, prior knowledge of existing technologies, size of company and portfolio, potential market for the product, and the stage of product lifecycle. The impact of the selected technology will then be weighed against the risk of successful implementation. Areas of focused innovation include process intensification, chemically defined simplified media, robust scalable harvest technologies, standardized modular approaches, and single-use technologies. L



In my December 2016 *Life Science Leader* outlook article sharing predictions for 2017, I argued it was going to be the year to watch biosimilars. Having arrived at the tail end of 2017, I stick by my original claim, though with a few exceptions. The U.S. and some European countries still have not seen significant biosimilar uptake or pricing competition. Major U.S. payers have been slow to offer up their prized primary formulary positions to biosimilars, while patients and physicians remain uncertain of or in the dark about biosimilars in general. But that doesn't mean there hasn't been any progress.

Over the past year, the industry has seen continued revision of the U.S. biosimilar regulatory pathway, additional biosimilar approvals, and competition-inducing launches. There also have been intensifying legal battles (and some significant settlements) and revisions to CMS' contentious reimbursement policies. We reached out to eight experts from biosimilar companies and consulting firms to see which topics they've been watching closely throughout 2017 and how they expect these trends will evolve and challenge the industry in 2018.

ANNA ROSE WELCH Editor, Biosimilar Development
@AnnaRoseWelch

2018: THE YEAR OF BIOSIMILAR COMMERCIALIZATION WINS OR WOES?

THE EARLY STAGES OF COMPETITION: NEW AND ONGOING HURDLES

Though there's still a long way to go, 2017 gave the U.S. a taste of a multi-competitor biosimilar market. In July, Samsung Bioepis and Merck launched the U.S.'s second infliximab biosimilar, Renflexis, to compete against Pfizer's Inflectra. But it wasn't the launch of two biosimilars for the same drug that was the most exciting part — it was the fact Samsung Bioepis chose to do so with a 35 percent discount (compared to Pfizer's 15 percent discount). So far, this has been the steepest discount to hit the U.S. market.

Next year glimmers with the promise of increased competition. As Adello Biologics' CEO Peter Moesta described, "If you take into account pending and anticipated biosimilar applications, we start to see the potential for multi-competitor markets in the U.S. for some of these targets near term."

But Moesta raised a few concerns about the challenges to market entry we've observed within the past year. Perhaps one of the most notable events in 2017 was Pfizer's lawsuit against J&J alleging anticompetitive practices, which, in turn, kept Pfizer's biosimilar from payer formularies and patients.

I've often found the biosimilar space to be one of the most exciting markets to write about because of the number of stakeholders involved. But Moesta's example touches upon one big downfall of such a wide base of stakeholders: They all have different goals and expectations for the fledgling biosimilar industry. "There is an additional layer of complexity in the U.S. market because the stakeholders who exert influence over which pharmaceuticals are used change depending on where and how the drug is dispensed," Moesta said.

So far, the biosimilar industry has been no stranger to practices that stand in the way of a competitive industry. We're all familiar with the "whisper campaigns" emphasizing the quality and long-term reputation of the innovator drug while touting the perceived (and currently unfounded) risks of biosimilars in quality and immunogenicity. As Carlos Sattler, VP of clinical development and medical affairs for Sandoz, described, these campaigns have continued to grow increasingly aggressive as biosimilar uptake has increased. But as he pointed out, we cannot forget about the 11 years of successful real-world experience with biosimilars in the EU.

"Sandoz has 340 million patient days of experience across 86 countries," Sattler said. In fact, since Zarxio was approved in 2015 and launched in the U.S. in 2016, there have been over 85,000 patients treated with the biosimilar. "Real-world experience affirms the FDA's statement that patients and healthcare professionals can expect the same safety and efficacy from an FDA-approved biosimilar as they do from the reference product," he added.

WHAT TO EXPECT FROM INTERCHANGEABILITY & BSUFA II IN 2018

We didn't have to wait long in 2017 for the FDA to release its long-promised interchangeability guidance. However, the agency's suggestions raised a few eyebrows. PA Consulting Group Life Sciences experts Chris Isler and Magnus Franzen said the interchangeability designation potentially could offer a "huge competitive advantage" since the biosimilar could be substituted at the pharmacy without the physician's permission. However, there are still a number of questions that need answered before these guidelines are solidified, they explained. Many of these questions concern the requirements for switching studies, the use of real-world data in determining interchangeability, and whether interchangeability should be sought on an indication-to-indication basis.

Molly Burich, Boehringer Ingelheim's associate director of public policy, biosimilars, pipeline, and reimbursement, said her company has expressed concern that some requirements may be "arbitrarily defined and burdensome." Much like Isler and Franzen, Burich expects biosimilar makers will face challenges determining how high the bar will be to prove interchangeability between the reference product and biosimilar.

In addition to interchangeability, the industry saw the successful reauthorization of the Biosimilar User Fee Act (BsUFA II), which authorizes the FDA to collect fees from drug companies for the review of biosimilar applications. Bruce Leicher, SVP and general counsel of Momenta Pharmaceuticals and chair of The Biosimilars Council, shared that he's "cautiously optimistic" the innovative reforms included in this legislation and the FDA commitment letter will accelerate biosimilar reviews and approvals. For instance, the FDA has promised to hire additional review staff, implement a longer review period to eliminate the need for extensions and increase the likelihood of first-cycle approvals, and provide additional communication opportunities between the agency and biosimilar companies.

In the past, the industry expressed concerns over the FDA's ability to ensure a timely review and approval process. As Gillian Woollett, the SVP of Avalere Health, pointed out, "Of the seven biosimilars approved by the FDA, the action dates were missed the majority of the time, and the performance is even lower if one counts the applications upon which no decision has been made." Now that BsUFA II has been implemented, she expressed hope the adjustment to the FDA's review period will help the agency better meet the action dates set for each biosimilar.

The experts shared the issues they faced throughout 2017 and spelled out how they expect these will challenge the industry in 2018. They also highlighted the trends they expect to see taking shape over the next year.

WHAT BIOSIMILAR TRENDS SHOULD COMPANIES PAY ATTENTION TO IN 2018?

"Securing reference product for clinical trials and the extensive comparative analytical work required of biosimilar developers has moved to the forefront as an important issue because failure to do so hinders developers' abilities to enter the market in a timely and cost-effective manner. Additionally, we hope to see the first biosimilars approved without the requirement of a Phase 3 clinical trial in 2018 and that the industry will continue to rally behind the inherent need to put science and analytical foundations first in a biosimilar development program.

PETER MOESTA
CEO
Adello Biologics

"It is likely we will see more patent licensing agreements, similar to those of Amgen's and AbbVie's over adalimumab, in large part because the costs of litigation become prohibitive. It also will become apparent that the 12 years of exclusivity granted to originator biologics is not currently the rate-limiting step to biosimilar availability, but exclusivity will likely continue to be part of the political debate nonetheless.

GILLIAN WOOLLETT
SVP
Avalere Health

"We should expect companies to begin to seek interchangeability designations for appropriate products. It is a bit too early to tell, but for some products, interchangeability could offer a competitive advantage due to the opportunity for pharmacy substitution and more favorable reimbursement.

BRUCE LEICHER
SVP and general counsel, Momenta Pharmaceuticals, Inc., and chair of the board of The Biosimilars Council

"As biosimilars are still new to the U.S. healthcare system, manufacturers will be challenged by several important regulatory issues over the next year, including:

- Scientific data requirements – how can "highly similar" be defined and proven?
- Naming and labeling procedures – what information should be included in the label and/or patient information? If biosimilar naming guidance is to include nonmeaningful suffixes, how will that impact the clinician's ability to track the identity of a biologic or a manufacturer's ability to track pharmacovigilance and safety protocols?

MOLLY BURICH
Associate director, public policy, biosimilars, pipeline & reimbursement, Boehringer Ingelheim

"We expect to see more attention paid to biosimilar prices (both in the EU and the U.S.). In some parts of the EU, we see prices coming down a lot, while the U.S. has been a bit more conservative. Given that price will probably play a huge role in the uptake of biosimilars in the payer community, this is a development to keep an eye on in 2018.

CHRIS ISLER
Life Science Expert
PA Consulting Group

MAGNUS FRANZEN
Life Science Expert
PA Consulting Group

"While not new, one issue is education and increased awareness, primarily directed at patients and healthcare providers. Balanced, accurate biosimilars education is the responsibility of industry, managed care, professional societies, trade associations, patient advocacy groups, and government. We must continue to champion policy and regulation changes that promote patient access to biosimilars.

CARLOS SATTLER
VP of clinical development & medical affairs, biopharma Sandoz

REIMBURSEMENT: NEW CMS POLICY A WIN FOR BIOSIMILARS

CMS sparked much criticism from the biosimilar industry with its original reimbursement policy for biosimilars in Medicare Part B and Part D. In Medicare Part B, for instance, CMS' original policy grouped all biosimilars for a single reference product under one J-code or billing and payment code. Momenta's Leicher said that this original policy "distorted the marketplace for providers," because it essentially treated non-interchangeable biosimilars as though they were interchangeable with each other.

Burich also pointed out some inconsistencies between CMS' previous Medicare Part B policy, which treated biosimilars as if they're generics, and Medicaid. For instance, under Medicaid, biosimilars are considered branded products and, as such, biosimilar manufacturers are required to pay the 23.1 percent rebate required of all branded products as per the Affordable Care Act (ACA). "These conflicting views are challenging for manufacturers, who — with the support of advocacy and patient organizations — will need to ensure reimbursement incentives for biosimilars are adequate to ensure their uptake and long-term utilization," Burich stated.

One of the ways Leicher and organizations like The Biosimilars Council argued CMS could alter the Medicare

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Part B policy was by adopting a unique code for each non-interchangeable biosimilar. And luckily, following a comment period on CMS' CY 2018 Revisions to Payment Policies Under the Physician Fee Schedule and Other Revisions to Part B, the biosimilar industry got its wish. CMS recently announced its plans to assign individual codes to each biosimilar starting January 1, 2018. For marketed biosimilars that are currently grouped into a common payment code, the agency expects it will take until mid-2018 to implement new payment codes.

WHAT CHALLENGES AWAIT THE BIOSIMILAR INDUSTRY IN 2018?

Depending on the role you play in the biosimilar industry, there are likely a number of specific challenges keeping you up at night. However, we're reaching a pivotal point when it comes to IP challenges. The biosimilar space may have triumphed in the Supreme Court case, Amgen vs. Sandoz, eliminating the extra six-month waiting period stalling market launches post-approval. But the industry should also note the recent settlement between Amgen and AbbVie barring Amgen's biosimilar Humira from the U.S. market until 2023. As such, I'd argue patent challenges and their settlements should be stepping closer to the front of your list of concerns.

As Adello's Moesta argued, market entry is going to be one of the biggest challenges facing companies in 2018 and beyond. Because the biosimilar market is still new to the U.S., there is much uncertainty about how patent battles will play out. "This uncertainty, combined with long development timelines and high investment, could further deter companies from entering the biosimilar market," Moesta explained. "We remain very concerned about how these IP battles will play out, particularly regarding the delay of market entry."

In fact, Isler and Franzen expressed concern over the potential "domino effect" that could occur because of delays from patents. For instance, some executives argue there is a one-month window for getting a biosimilar on the market, and this brief window is enough to set you on the right or wrong side of a successful biosimilar business case. As they describe, the longer a biosimilar is held off the market because of patent challenges — whether it be just a few months or even years — the higher the cost of market entry will be. This, in turn, impacts the margins for setting a price, which is the vehicle for determining how competitive a biosimilar will be, how quickly it will gain a foothold on the market, and how great its market share will be.

Though more biosimilars have been approved than launched in the U.S. because of lingering originator patent challenges, Leicher expects to see launch and patent timelines become more streamlined in the future. He noted, "As more products are approved, we should see a convergence of regulatory and launch dates as greater experience with *inter partes* review at the U.S. Patent and Trademark Office and the biosimilar patent exchange and litigation process enables applicants to estimate regulatory and patent clearance timelines for each product more reliably."

But Leicher's point about companies getting better at managing timelines brings up what will continue to be a key challenge facing companies in 2018 and far into the future. Each of the eight experts interviewed for this article touched upon the challenge of establishing a commercial model and ensuring a competitive market. But Woollett said it best when she argued that companies will need to break from tradition in the ways they approach the industry. Companies will need to ensure that all participants understand the importance of a long-term, multisource sustainable marketplace.

"Too much short-termism will irreparably harm this industry and the prospects of real competition before it even starts," she warned. "This is a very real risk which also carries a liability for originator companies whose actions could be interpreted as overly protectionist or anti-competitive. We're already seeing experienced biosimilar sponsors trimming their portfolios of biosimilars, and competition is being curtailed before it has even started — especially in the U.S."

Because biosimilars are not brands, nor are they generics, companies face the daunting task of establishing a new commercial model best suited to these sophisticated new treatment options. Woollett expressed optimism that there can be more than the two primary brand and generic commercial models. But she urged the industry to take a close look at the dominance of these two leading commercial models as the biosimilar industry attempts to forge its own.

Because resources between the innovator and generics and biosimilar industries are so asymmetrically distributed, "We have to be careful not to presume biosimilars can survive and flourish to create a sustainable multisource market in the U.S.," Woollett argued. "Remember, even Europe struggles with the sustainability question. This may take some serious thinking about the bigger commercial and regulatory environment and the nature of the incentives impacting each decision maker in the chain from manufacturer to patient. Biosimilars should play a significant public health role in the U.S., including in savings for systems/patients, in earlier access during disease progression, as well as in surety of supply. But at this stage, that is still far from assured." L

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VIRTUAL & VARIABLE:

Two Visions For Biopharma Outsourcing In 2018

ROBERT DISCORDIA
Executive Director, Global Product Development & Supply Procurement
Bristol-Myers Squibb

DEBORAH DUNSIRE
CEO
XTuit Pharmaceuticals

LOUIS GARGUILO Chief Editor, Outsourced Pharma @Louis_Garguilo

Regarding the trends identified by the biopharma executives interviewed for this discussion on the state and future of outsourcing, I'm reminded of the tongue-in-cheek reply as to why people — and organizations — make some of the decisions they do: "Because we can." Perhaps a better way to say that is, because they have become enabled.

In our case, we are witnessing decisions to create new biotech models for drug development and new approaches to externalization at pharmaceutical companies, because outsourcing has become a multifaceted and trustworthy enabler. Outsourcing today de-risks creation through externalization. Biopharma executives are now empowered to formulate these new business and operating models to pursue both financial and scientific objectives.

When I asked Deborah Dunsire, CEO of XTuit Pharmaceuticals, if she would have thought 15 years ago we could partake in external partnerships as we do today, it drew the most emphatic response of our conversation: "No, certainly not!" And she's one of the more experienced and visionary professionals in our midst, having previously been president and CEO of both FORUM Pharmaceuticals and Millennium (Takeda), and before that a longtime thought-leader at Novartis. (See our November 2017 "Explorers Blaze On" article on Dunsire.) Now at the reins of XTuit, she's taking part in what she identifies as the biggest influencer of our drug development industry: virtualization of biotech and technology-based companies enabled by external cooperation and expertise.

For Robert Discordia, whose own career spans over 25 years at Bristol-Myers Squibb, including the last four as executive director, global product development & supply procurement, when it comes to the future of drug development and manufacturing outsourcing — and the relationships between drug developers and service providers — the focus is on a different "V" word. "Variabilization," he says, "will intensify." It's an awkward word for an enabling strategy growing more elegant as large pharmaceutical companies continue to expand its application. Discordia offers a simple definition: "Variabilization is the process by which fixed costs are transformed into variable expenses." He adds that an interesting subfactor in this transformation — an enabler of its own — is another intensifying trend in our industry: mergers and acquisitions, including those between drug owners and CMOs.

So as we look to 2018, let's start with Discordia's discourse on variabilization and then circle back to Dunsire's dissection of the continuing virtualization of the biotech model. We'll learn that these trends dovetail and, via more intimate external partnerships, lead us to new vistas for drug development and manufacturing outsourcing.

VARIOUS WAYS TO VARIABILIZE

"In the pursuit of greater efficiencies throughout the pharmaceutical industry and a concerted push for earnings growth, we are likely to see two major trends in 2018," says Discordia. "Pharma is focusing on increased variabilization of operational costs, and in a related development, we should see a continued consolidation and simplification of each pharma's respective supply networks." In other words, more outsourcing with less complexity. How will that work?

First, the focus on increasing variabilization starts with what Discordia says is a "hard and holistic look at all the constructs within a respective pharma company, in order to fully reconcile whether each serves as a core function that the company has no option but to possess." An anticipated output of these in-depth investigations could be an even higher reliance on contract service providers of all kinds. Executives at drug companies are becoming better at discerning their core needs and recognizing the opportunities to transfer those costs to partners. These enhanced investigations have occurred independently across the industry over the past years, says Discordia, and also have added to the gradual expansion and maturation of the CDMO industry. That expansion has now reached critical mass, pushing the industry to take actions that will ensure it can handle the ever-increasing project load. "We've seen this maturation manifest itself in capabilities, quality systems, expanded service offerings, and a higher level of sophistication overall," Discordia explains. "It's brought our industry to a tipping point, where these now highly competent and reliable CDMOs rival, and in some cases, outpace capabilities within drug owners' operations."

This tipping point has emboldened Big Pharma to selectively sell off manufacturing assets to CDMOs and then enter into strategic, long-term supply and product-management agreements with the purchasers. The CDMO, "By nature of its theoretic ability to more efficiently fill the facility with projects — and thus improving the utilization factor — can supply product back to the seller at a reduced cost." The resultant product-cost benefit is in addition to the more fundamental fact that this act of variabilization removes all the costs of owning and managing facilities from Big Pharma's balance sheets.

At the same time, pharma has worked to streamline supply chains and thereby reduce overall internal operational costs of product and business management. Discordia believes this will likely cause "the continuation of supplier-selection strategies focused on extracting greater value from a fewer number of strategic partnerships." Key to achieving these efficiencies is up-front, internal engagement and close collaboration between an organization's operations and sourcing functions. Discordia notes, "The operations and procurement functions at BMS work hand-in-glove to ensure we have aligned strategies and streamlined internal processes."

Furthermore, Discordia says this enlarged strategy of streamlining and externalizing more assets and fixed costs becomes part of a rigorous "total value of ownership" approach. It's an all-encompassing strategy "to truly reduce operational costs, while at the same time providing greater autonomy to suppliers — and therefore holding them to greater accountability — and allowing them to generate additional value." All of this seems consistent with what CMOs say they want: more freedom to operate, shared responsibility, and higher profitability from high-value and dedicated customers. Both sides should be able to reduce their overall business complexity and improve outcomes.

Discordia does, though, sound a single warning: "Continuation of these trends over years could lead to a large polarization in the demographics of CDMOs, as Darwinian M&A continues to select the stronger and more valuable suppliers and leads the others into minority positions or even forced exits." But for the most part, he sees these trends as positive and growing. He notes the recent $7.2 billion purchase of Patheon by Thermo Fisher Scientific, "creating the largest and most end-to-end CDMO currently in the industry," as an example of an M&A that could open up more variabilization opportunities for drug owners.

A VIRTUALIZATION VIRTUOSO

Pharma outsourcing of manufacturing dates back decades, but the engine that propelled us onto this high-speed autobahn of externalization was really the first decade of the 2000s. That's when, among other developments, drug patent expiries (our so-proclaimed "patent cliff"), began to lead Big Pharma to fundamental structural reviews.

First among the changes at larger pharma companies was a comprehensive transference from internal to external discovery and development models, as well as an ever-increasing focus on the manufacturing of API and drug product. As important — and perhaps the real revolution — was the confluence of these economic and business realities, with breakthrough scientific advancements that also burst onto the scene (think ADCs, cell, gene, and immunotherapies). This helped create an invigorated external-support industry, which early-stage companies could also readily tap into. So where our industry used to have "biotechs," we now spawn "startups," predominantly based on the highest possible degree of virtualization — the fewer employees and hard assets, the better.

Dunsire sees these trends strengthening. "There will be more virtualization, well beyond today's established manufacturing partnerships or certain pillars in drug research and development," she says. "Perhaps one way this will advance is with experienced drug developers from industry taking positions at CROs, enabling drug sponsors not only to outsource the execution of clinical trials but also to receive a full-service solution. This could include the opportunity for drug sponsors to partner with clinicians with a tremendous amount of drug development experience in clinical strategy. Until now, that expertise and reliance was something that remained within the drug companies themselves – for good reason. But in the future I see a bigger offering from the CROs to inexperienced drug developers."

Dunsire does add a qualifier: "This will still require additional changes to attitudes and business models, particularly regarding the partnerships to spur the growth capabilities at the contract partners." These new kinds of partnerships, she says, are key to continuing the overall trend of virtualization of drug developers. "When I think about where I currently stand in XTuit — an early-stage company — I know the partnership aspect must grow up as we advance as a company and as our pipeline advances. Today it should become a hand-in-glove relationship starting early in the drug development phase. Our CDMOs are feeding us ideas on how our process is working and how to obtain a higher yield and more efficiencies."

Moreover, Dunsire says early-stage companies are not only more virtual than ever before because of this collaboration, but also they can remain that way for a longer period of time. "This allows for the formation and expansion of new types of companies, and it allows them to reach a critical mass before they need to internalize particular functions. Yes, there's always going to be a need to add some professionals within the drug company, but today their function is managing the selection of external suppliers to forward the work and performing specific troubleshooting." With process chemistry, for example, Dunsire says a company can remain, well, virtually virtual, "while the critical internal element is having a person with sufficient experience and expertise to understand how to operate with those contract partners."

Of course it all starts with selecting the best partners, those who have the right teams in place, but also whose business models mesh with the virtual drug developer. "Does the CDMO actually have the ability to work with smaller companies on process development?" is an example of a fundamental question, says Dunsire. "Because still today, certainly not every supplier is willing to work with virtual companies. Those that do are betting — and they're right — that if you work well together and establish the process to get to clinical supply and ultimately commercial, that same partner will have been, and continue to be, your supplier."

THE FINAL VISION

We started our discussion talking of enablers. But as mentioned directly above, there may not always be willing partners waiting in the wings. Sometimes — for example with new technologies and platforms — enablers don't yet exist. Therefore, Dunsire says, for the modern-day startup, even at the stage of precompany formation, the scientists, entrepreneurs, initial board members, and financial backers need to determine whether, in fact, partners are out there. "Folks who have been in the CAR-T or mRNA (messenger RNA) space, like Arie Belldegrun of Kite or Stephane Bancel of Moderna, have told me they decided that manufacturing internally was a critical element to be successful," she explains. "There simply were not established processes or experienced service providers to work with." For that type of leading-edge technology, "They realized building and manufacturing was a strategic component to actualize the opportunity for these technologies to become therapies." Another example she provides is the onset of the antibody-technology companies some years ago. "Companies that adopted that approach to antibody therapeutics had to grow most of the expertise in-house," recalls Dunsire. "So even today, sometimes innovators will have to build out the organization themselves." However, she quickly adds, "Sooner or later, the service providers will come along for the next generations of virtual companies in these fields."

So as with all trends, we can bet on experiencing certain adoption cycles, new hurdles and opportunities, and perhaps some missteps along with mitigating circumstances. Don't forget Discordia's warning that too much M&A might grow service providers to sizes where they are no longer interested in assisting the new startups and virtuals and snuff out some that are. Nonetheless, it seems certain both virtualization and variabilization will continue to move forward. In fact, when you think about it, isn't variabilization simply a form of Big Pharma virtualization? Discordia sums it up for both big and small companies. "These trends have the potential to transform the nature of competitive advantage by shifting the emphasis to competing on agility, value-chain orchestration, and risk management." Key, then, to both variabilization and virtualization, and to big and small companies, is unleashing the creativity enabled by new outsourcing partnerships in drug discovery, development, and manufacturing. L

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WHY ALL THE TALK ABOUT REAL-WORLD EVIDENCE?

ED MISETA Chief Editor, Clinical Leader @EdClinical

BRIAN CUFFEL
VP & Market Access
Head Of Oncology
Bayer

WILLIAM DALEY
VP of Medical Affairs
Sanofi U.S.

In 2017, real-world evidence (RWE) became the topic everyone wanted to discuss. At the DIA Annual Meeting in June, it seemed to be a clinical trend on the minds of many CROs. Several executives I have spoken to recently believe it will continue to grow in importance as we move into 2018 and beyond. But why the sudden interest in RWE?

Brian Cuffel, VP and market access head of oncology at Bayer, and William Daley, VP of medical affairs for Sanofi U.S., see several factors driving the interest. First, regulators, namely the FDA and European Medical Agency, are paying more attention to RWE than ever before. Both men believe the impact of RWE will be seen in the pre-approval process where this data will help to cut drug development timelines.

"By using RWE, regulators can really accelerate novel agents through the approval process and into the hands of patients," says Cuffel. "RWE supports their decision making in a way that was simply not possible in the past. It's an important new development, in oncology in particular, and, as such, interest in it is likely to grow."

Daley adds that RWE is a perfect complement to the data already generated during clinical trials. Although, he cautions that this trend is still in its infancy and notes that even with all of the current excitement and enthusiasm over RWE, it will take more time for it to make an impact on regulatory approvals.

Are Your Products Truly Effective?

Daley believes another factor behind the push for greater use of RWE is the desire for safety and effectiveness data on patients who are not part of a clinical trial.

"Clinical trials are not always applicable to the general population," he says. "Inclusion and exclusion criteria will keep many patients from being able to participate in a trial, due to the need for a clean population that will not introduce bias into the study. But once the product is made available to the general population, we can really begin to gauge its effectiveness. Understanding the effectiveness of new products at this stage is of paramount concern for both regulators and sponsors, which is driving the trend of collecting more RWE."

Daley says being able to see the impact of a drug on people in their everyday lives — how they take the product, what it does and doesn't do — all of that can be very different from what you see in a controlled population in a clinic.

Technology advancements in drug development also are sparking interest in RWE. Cuffel notes advanced healthcare analytics coming from IBM's Watson and companies such as Google are helping to transform the industry. For example, IBM's Watson will enable companies to integrate data from all sources in the clinical trial ecosystem, including EMRs, healthcare professionals, patients, data managers, and sites. Additionally, insurance companies, particularly in the U.S., are looking for medicines that can demonstrate improved patient outcomes and reduce hospitalization rates and length of stays. There is also an industrywide effort to bring more personalized medicines to market. All of those efforts are generating valuable data and creating a strong argument for adoption of RWE in more trials.

"Payers want to understand the effectiveness of a new drug on the general population, so they gain better insights into what they are paying for," says Daley. "Payers need to understand the benefit to patients, as well as which patients are most likely to benefit from the treatment. Even policymakers will look at the results of trials to make decisions." In short, there is almost no stakeholder in the drug development process who would not benefit from the additional insights that can be gained from RWE.

How Do We Gather The Data?

In years past, RWE was generally gathered in a Phase 4 (post-approval) trial after a treatment was approved by regulators. That is no longer the case. In many trials, particularly in the area of oncology, this data is being gathered while the treatment is still in the clinical phase. The data is expected to strengthen the evidence gathered relating to the efficacy of new drugs and bring additional validity to new drug applications submitted to regulators.

"In oncology, evidence leading to regulatory approval can sometimes be an extension to a Phase 1 study," says Cuffel. "RWE can be very helpful in providing access to historical controls on standard of care. By combining RWE with new data we have on our molecule, we can help accelerate that regulatory decision-making process. The process of RWE generation can then be extended into the post-approval phase, subsequent to a conditional approval of the molecule. This will help increase patient access to the medicine while companies continue to generate additional RWE on the safety and efficacy of the drug."

Cuffel and Daley agree that gathering the evidence prior to regulatory approval is done via a combination of clinical trials and early-access programs. The goal of RWE is to generate comparative data on standard of care and to demonstrate how the new treatment being advanced is better than what is currently on the market. That makes Phase 1 and Phase 2 trials a good place to gather additional data that could assist with approval or even planning of the Phase 3 trial.

Diversity is one key factor outlining the importance of gathering RWE early. In a clinical trial, it is often difficult to predict what the effect of a drug will be on patients of diverse genders and ethnic backgrounds. The reason for this is the lack of representation in trials of many of those groups.

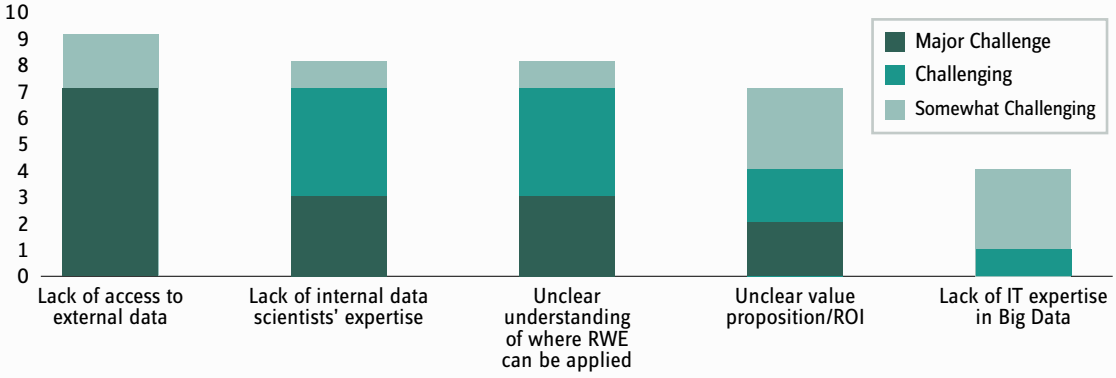
"Even in a clinical trial with 15,000 or 20,000 patients, you might be lucky to have a couple hundred individuals of Hispanic or African American descent," says Daley. "It would be difficult to make any statement about the effect on those 200 patients in a 20,000 patient study. Having RWE is a much better way of determining a product's effectiveness in various ethnic populations. With RWE, we have a much more robust data set from which conclusions can be drawn.

A Perfect Match With Patient-Centricity And Big Data

As companies begin to gather RWE, they also will be entering the world of Big Data. Cuffel notes that one of the biggest opportunities presented by Big Data is having an increasing amount of clinical evidence on entire populations. We know different types of patients respond differently to treatments. Unfortunately, in clinical trials we often do not have a great amount of patient diversity. RWE allows pharma to better see the effect of medicines on women, African-Americans, Latinos, and other groups that tend to be under-represented in clinical trials.

"RWE will allow us to look at a meaningful level of patient numbers and see exactly what treatments patients are receiving and at what dosage levels," says

WHAT ARE THE CHALLENGES TO IMPLEMENTING RWE PROGRAMS?



SOURCE: Deloitte 2017 RWE Benchmark Survey

Cuffel. "This then allows us to determine which treatments benefit which patient groups the most. We also can look at combinations of treatments, an increasingly important area in oncology that is helping us create the most benefit for patients. That can be done only with large samples of patients."

"The data we get from study participants in real-world settings allows us to see what they are thinking," Daley states. "Patients tend to talk about what is important to them. It's those comments we get from analyzing RWE that help us create better designs for future trials. We also can use that information to better recruit patients and increase the overall level of patient involvement in clinical trials."

Cuffel adds that RWE can help pharma better understand areas of unmet need, especially for patients receiving treatment with commercial therapies and standard of care. Pharma benefits from learning how to produce better protocols and inclusion/exclusion criteria, which leads to better patient recruitment and, ultimately, patients who are more engaged throughout the study.

Clearly, being able to provide patients with a treatment they are more likely to respond to could be considered the most patient-centric of all approaches. The ability to mine that data and use it in drug development to test therapies on the market against various biomarkers will be an area of great opportunity for both sponsors and patients. According to Cuffel, those abilities also will take the industry to a new level of patient-centricity.

Not Just For Oncology

While RWE seems to be a great fit for oncology studies, its use can span all therapeutic areas. When it comes to the use of RWE, Cuffel believes cardiovascular disease is the area that leads all others. In the cardiovascular field, information for the primary trial endpoints is often available in healthcare claims databases. But in oncology that is not the case. Researchers had to wait for the evolution of more sophisticated clinical data, which now has become a reality.

Daley agrees that RWE is applicable to all therapeutic areas. He notes that in 2012 there were questions surrounding a Sanofi diabetes drug and whether it presented an increased risk of cancer. For that insulin drug, Lantus, Sanofi performed a very large RWE study to understand whether the risk was real. That study involved 12,000 patients and found no association between Lantus and cancer. Three additional studies supported that finding.

The data from any clinical trial can contain collection errors, typos, outliers, and other anomalies that must be cleaned up prior to regulatory submission. The situation can be even more pronounced when dealing with data from the real world. In the real world, you do not have randomization of treatments to patients. A patient will get what their physician prescribes for them, and that treatment is impacted by a wide range of factors. Conversely, the outcome also is going to be affected by a multitude of factors, not just the treatment itself.

"I expect many of the major pharma players to increase their investment in RWE," says Cuffel. "It will continue to be a growing trend into 2018 and beyond."

Nevertheless, he's quick to note that there will be challenges related to how the data is collected and its consistency. "Pharma will need greater expertise in analytics and Big Data, and many companies will need to add qualified analytics groups to correctly review the data. For many companies, RWE is still a new concept, but everyone will see its advantages and get better at implementing it."

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7 MEDICAL DEVICE LEADERS

Talk About What's Next For Their Industry

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Who could have known a year ago that Becton Dickinson would purchase C. R. Bard for $24B or that Abbott would acquire St. Jude Medical for $25B? Who would have guessed the long-awaited new medical regulations would be enacted in Europe? Those positioned as leaders within the industry would be most likely to have seen those types of things coming, since they are heavily involved in what is going on and often connected to the ones making those decisions. I asked the following medtech leaders what changes they expect to see as we move forward into 2018.

WHAT WILL THE FUNDING CLIMATE LOOK LIKE FOR THE MEDICAL DEVICE INDUSTRY IN 2018?

Doug Bernstein: Foregoing any big jolts to the market, I don't see a huge change to the funding climate. I think the main driver is going to be the maturing of certain technologies (e.g., transcatheter valves); however, some of the segments that have consistently been exciting but early (e.g., tissue engineered devices) I continue to see as early. I think it remains to be seen how some of the large-scale consolidations, such as Abbott/St. Jude, BD/BARD, or LivaNova, are going to affect the industry, but we may still be waiting through the next year to see major effects. We could see more of a scramble to compete in certain segments such as the transcatheter mitral valve space (to an extent we already are), and that could be fairly interesting.

Pete DeComo: It will continue to be challenging. The earlier the stage of the company, the more challenging it will be. VCs have become more like growth-stage investors not wanting to take the early risk associated with product development and regulatory approvals.

Matt Kesinger: The regulatory environment for med devices in the U.S. is improving. The pendulum has swung back. Med device investors started leaving the industry as the regulatory burden increased and clearance became less certain. Now that clearance times are decreasing, I think investment will start making a comeback.

WHAT DEVICE SEGMENT WILL BE GETTING ALL OF THE ATTENTION IN 2018? WHY?

Maria Bennett: I believe neurostimulation is becoming a critical game changer in the field of pain relief/management. In 2018, you can expect more doctors and patients to adopt and use devices specifically designed to preferentially activate target nerve fibers,

delivering sustained, significant pain relief without opioids, surgery, permanent implants, or tissue destruction. The popularity of neurostimulation is, and will continue to be, driven by the tremendous need to offer the millions of pain sufferers worldwide nonnarcotic therapies for pain relief. Look no further than the ongoing opioid crisis, which has been devastating in my home state of Ohio (and beyond), for the need for innovative pain relief therapies such as neurostimulation to become treatments of first, not last, resort.

David Groll: Digital health will remain strong because of the lower regulatory barriers and potentially faster exits.

Maureen Mulvihill: Digital medtech is going to continue to be big news next year. This is such an exciting and dynamic area in healthcare right now. We've seen an explosion of wearables that provide individuals personalized healthcare information, and as researchers across the world work to harness Big Data to find healthcare solutions for entire patient populations, digital health is transforming how we think about and deliver healthcare every day.

WILL MEDICAL DEVICE M&A ACTIVITY INCREASE, DECREASE, OR STAY THE SAME IN 2018? WHY?

DeComo: Stay the same. Acquirers are waiting longer to acquire, attempting to mitigate as much risk as possible. FDA approval is almost a must-have, and some commercial traction is strongly desired.

Groll: It will stay the same; the innovation pipeline is going to remain constrained because of lack of early-stage funding. This will impede acquisition activity. If the economic expansion ends, there could be consolidation (mergers) among the large companies.

Mulvihill: I expect M&A activity to increase slightly in 2018. We are seeing evidence of truly innovative products (e.g., premarket approval [PMA] and de novo pathways) generating greater up-front multiples and quicker times to exit than the more iterative traditional devices (e.g., 510(k) path). Large companies also are opening up to more earlier-stage strategic partnerships, as previously discussed, which could drive greater M&A activity. However, continued consolidation in the industry and the overall environment for medtech investing are limiting factors.

WHAT CHANGES MIGHT WE EXPECT FROM THE FDA IN 2018?

Bernstein: I think a lot of focus has been on how regulatory changes elsewhere are going to affect the industry (i.e., revision of the Medical Device Directives in Europe is the big one, but also changes coming to India's regulations and elsewhere). There has been so much speculative noise with the new administration that it is difficult to predict how potential changes may play out (or even if potential changes will be made at all). However, it seems more likely that we may see assessment of medical devices in Europe via the CE mark come more into line with 510(k) clearance, and if that happens it would have a significant impact on markets.

Groll: Difficult to say. On the one hand, there seems to be some effort to integrate new technologies into the FDA framework in a sensible way. On the other, the agency seems to be even more arbitrary when it comes to enforcement in some of its traditional areas.

Maria Fagan: In general, the FDA has been trying to become more transparent and more responsive to industry. Statistics have shown a reduction in review times for both 510(k) and PMA devices, providing evidence of the movement in this direction, and the FDA is much more helpful when it comes to resolving issues. The use of the presubmission process has been very helpful to fully understand the FDA expectation well in advance of a submission so that companies can align on what is needed. Additionally, the FDA has several initiatives to improve innovation, some stemming from the 21st Century Cures act passed in December of 2016. Overall, I think there is movement toward more responsiveness and reasonableness and the use of real-world data to assist with FDA clearances and approvals. In contrast to the FDA, where they are becoming more reasonable, the release of the EU medical device regulations in May 2017 indicates the seriousness of the EU's concern with the safety of their devices. The changes are expected to tighten down on notified bodies (organizations designated by an EU country to assess the conformity of products before being placed on the market) and, consequently, to ensure the intent of the regulation is upheld. During the transition time of the EU MDR (medical device regulations), there will be confusion, and companies will likely hesitate to enter the EU unless really needed.

WHAT ARE SOME UPCOMING CHANGES RELATED TO CLINICAL TRIALS FOR MEDICAL DEVICES?

Bernstein: It will be interesting to see how some of the high-profile trial spaces play out. Enrollment alone is a big question for the more disruptive spaces, and all of the companies scrambling to start only make that harder. Couple the large amount of uncertainty of outcomes with a new type of device, and I think we have an uncertain picture. One big trial failure could have a ripple effect, whereas I think it will take years to build the type of evidence that will start to bring confidence.

DeComo: It is for real. In our case, we were approved in Canada and the EU in 2013. Based on the FDA requirement that we conduct a PMA trial, we most likely will not be in the U.S. market until late 2019. Should it really take the U.S. seven or more years for the FDA to be convinced a device is safe and effective?

Mulvihill: Certainly the proliferation and sophistication of data collection is going to be a trend to watch when it comes to clinical trial evidence. As part of the new user-fee agreement signed into law, the medtech industry committed to funding several premarket pilot projects for the agency's National Evaluation System for health Technology, or NEST, to explore whether use of real-world evidence could help the FDA determine whether a device could be eligible for an expanded indication for use and other premarket activities. There could be some very exciting opportunities regarding the use of real-world evidence, and the industry looks forward to working with the FDA and the NEST Coordinating Center to implement and evaluate these pilots as efficiently as possible. The FDA also released final guidance on the use of real-world evidence, which should provide helpful information to firms on the potential benefits of real-world evidence for premarket uses.

WILL MEDICAL DEVICE COMPANIES OUTSOURCE MORE OR LESS IN 2018? WHY?

Bernstein: I don't see a strong trend toward bringing manufacturing in-house short of some major legal/regulatory changes. Especially for small companies, I think there is a lot of danger in growing infrastructure too fast, and I don't see the current uncertainty changing that. Still, I think the status quo is always a strong argument for highly regulated devices given the time and cost of making changes, so I don't necessarily see there being a strong trend to try to outsource more either. I think the recent bout of large-scale consolidation is not indicative of a substantial appetite for risk right now, so I wouldn't think we'll see major changes either way.

Groll: More outsourcing. There is a long-term trend toward specialization that encourages companies to outsource any noncore activities.

Mulvihill: The FDA's recent increased levels of scrutiny and rigor will likely decrease outsourcing of medical-device components and assembly to countries with low levels of compliance. Wage increases in countries such as China further lower their competitive advantage over U.S. manufacturing. However, there is an opportunity for low-labor-cost markets as end-product cost competition continues to intensify, if compliance can be improved. Companies will continue to balance capital investment and development costs against per-item costs and speed-to-market in the make/buy decision. Smaller firms must also carefully consider product life cycle and the potential for future products in the pipeline to utilize in-house capabilities.

WILL THE MEDICAL DEVICE INDUSTRY BE ABLE TO FIND THE TALENT IT NEEDS TO GROW?

Bernstein: I know that we find it difficult to an extent. The medical device industry requires all the talents of any other tech industry but without some of the "sexiness" of the currently popular ones. Since this has been the case for some years, I do think there is a bit of a shortage.

DeComo: To a certain extent it is region-dependent. Where there are larger anchor companies employing engineers and there are schools of engineering, it is not too challenging. However, seasoned engineers are generally hard to find and attract. We need to do more to encourage students to enter the engineering field, and the fact is, we are falling behind globally.

Mulvihill: Yes, because it offers greater purpose and industry stability. Millennials are driven by greater purpose; they seek to make an impact in the world. To attract the best and brightest, medtech execs need to showcase how their companies make lives better. Staff can also be found from the other three generations that are looking for a company where they have purpose and stability. These senior people have significant expertise and experience. By focusing on education and mentoring, the millennials will stay engaged as they are learning and growing, and their senior peers will stay engaged as they are valued for their experience and expertise.


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How To Lead, Succeed, & Thrive In 2018

DR. LIZ BYWATER

DR. LIZ BYWATER helps healthcare leaders increase influence, catapult innovation, accelerate growth, and build exceptional teams. She is the author of *Slow Down to Speed Up: Lead, Succeed and Thrive in a 24/7 World!* liz@lizbywater.com

How do today's healthcare executives stay focused on the right things, productive in the face of immense pressure and competing demands, and proactive and strategic in the way they lead? It all starts with taking a pause.

In my work with executives across the healthcare universe, I advise leaders to step back from the daily busyness, to reflect on where they are today, and determine how they will lead the way to a brilliant tomorrow. As we round the bend on 2017, I'd advise you, too, to take a strategic pause as you lay the foundation for a thriving 2018. Pause, reflect, engage your team, and address the following:

1. HOW DID WE DO?

Did we demonstrate resilience in the face of challenges?

Did we develop creative solutions to the problems of the day?

Did we successfully drive toward a brighter future?

2. WHAT KIND OF FUTURE ARE WE GOING TO CREATE?

What does a resoundingly successful 2018 look like?

Where are we, and the industry, headed in 2018 and beyond?

Are we cultivating the right talent, leadership, culture, partnerships, strategy, and innovation to get ahead of the curve?

What can we anticipate in the political, economic, regulatory, and competitive landscape?

Which factors can we control?

Where can we influence, and where can we lead?

In which ways, large and small, must we be prepared to adapt?

3. WHAT ARE THE (REAL) PRIORITIES?

Get exceedingly clear on what's important. Your long-term vision should drive the strategy, and your priorities will emerge from there. Each decision and action must move you closer to reaching your top goals. Strategic leadership requires that you avoid distractions and say no more often than you say yes. Invest your time, energy, and funding where they will have greatest impact—and let go of the rest.

4. WHERE DID THINGS GO WRONG?

Where and why did we fail?

What are the common denominators?

How will we avoid repeating the mistakes of the past?

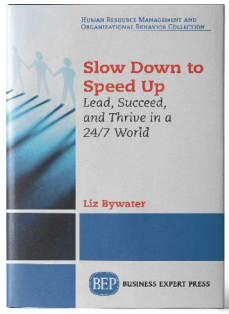
Past mistakes can provide tremendous learning. While it's unhealthy to stay mired in the past, it's worse to disregard the lessons you can glean from failures. Engage your team, partners, and customers in the hard conversations about what went wrong and why. That kind of robust, candid dialogue is essential if you are to prevent regrettable repetitions—the kind of repetitive errors that create unwanted complications, wasted time, and serious costs.

5. HOW WILL WE REPLICATE SUCCESS?

Where and how have we been most successful?

How can we understand our achievements and then replicate and expand upon them?

Be sure to recognize the people who've created the most successful outcomes. Launch the new year with your strongest leaders and top performers sitting in the right roles. Put them in charge of your most promising projects, enlist them to mentor others, and bring them together to drive collaboration, innovation, and transformation. That's the fastest way to extraordinary success in the new year. L



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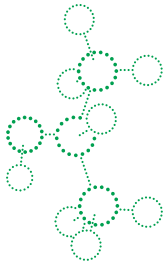

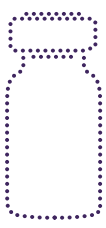

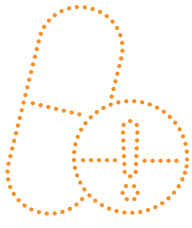

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Tufts Study Uncovers the Economic Advantage of Single-Source Drug Development and Manufacturing

Historically, large, established companies had their own internal end-to-end solution to see a project from development to proof-of-concept (POC). As portfolios diversified, this solution was no longer internally effective given costs and need for varied skills. As a result, the CDMO industry was established to offer a solution that provides expertise across therapeutic areas and formulations. As the CDMO industry was formed, it met a need along the development to commercialization process. CDMOs are now integrating and providing end-to-end-solutions. Integrated solutions offer a single-source solution, in which the sponsor partners with a single CDMO to create and deliver an integrated outsourcing approach that promises potential time and cost savings.

With healthcare costs continuing to rise, it is critical to assess the economics of both outsourcing models and ensure the one you select provides the most efficient path to commercialization. This was the purpose of a recent study by the Tufts Center for the Study of Drug Development (CSDD), which compared cycle times and development economics between multi- and single-source CDMO models. Rebecca Holland New, EVP, Business Management and Enterprise-Wide Operations at Patheon, a part of Thermo Fisher Scientific, which sponsored the study, explained the company's reason for having its model evaluated by a third party. "As we track industry trends, we see the cost of drug development increasing, with sales per asset decreasing at a faster rate. It is critical for us to understand the economic benefits for our clients under a streamlined, single-vendor outsourcing model," says Holland New. "Our internal research projected we could cut between 8 and 20 weeks off our clients' drug development timelines. It was important we validated the concept with a third party who could look at our data and provide a more precise measure based on risk, net present value, and total net gain."

> "By focusing on time as a primary value driver, a sponsor can lower the overall cost of bringing its drug to market, and more importantly, achieve the speed-to-market patients both want and need."

While there are many studies that debate the total cost of drug development,[1-3] the Tufts study sought a better understanding of which model offered the most accelerated time-to-market for its clients. By focusing on time as a primary value driver, a sponsor can lower the overall cost of bringing its drug to market, and more importantly, achieve the speed-to-market patients both want and need.

A closer look: multi-source approach versus single-source solution

According to Tufts, the research team looked at data from five single-source outsourced development and clinical trial manufacturing projects: three biologics (monoclonal antibodies) and two small molecule chemical entities. It also took into consideration the benchmark results on biopharmaceutical R&D costs and net returns for new biopharmaceutical approvals. Because vendor fees can differ by model, the sponsor fees used in the comparison were based on what the cost of each individual manufacturing process would be, depending on whether they were incurred under single- or two-source contracting (one CDMO for drug substance and one for drug product).

For model comparisons, the following assumptions were made (as gleaned from the study):

- Single-source or multi-source contracting is applied across a diversified portfolio of investigational molecules for a given clinical phase
- Reductions in the length of the contracted manufacturing processes translate to initiation of a clinical phase sooner than it otherwise would by the reduction in the amount of time needed to manufacture supplies for clinical testing, but the lengths of the clinical testing phases once initiated remained the same
- Net cash flows after approval remain the same, but they begin earlier according to the reductions in development phase lengths resulting from a different sourcing model

Upon comparison, Tufts concluded a single-source solution can shorten a drug development timeline by an average of 14 weeks less than a multi-source solution, with manufacturers pursuing a small molecule drug (in Phase 1) saving up to 19 weeks. Holland New explains this can be achieved by, among other factors, cutting out the time needed to make decisions about— and with—multiple vendors. "The Tufts study shows there is a time factor involved to evaluate, audit, and/or qualify vendors and then to negotiate processes and rates

with each provider," she says. "Single-source allows you to skip the time it takes to make those decisions and instead allows the precious resource of employees within your company to focus on the strategic elements. This is as opposed to getting into multiple discussions around which vendors to select and what each one's responsibilities will be."

With a faster drug development timeline, single-source CDMO contracting can provide substantial financial gains to drug sponsors when applied to a portfolio of investigational drugs. On average, gains from reduced preapproval development costs and increased net revenues after tax were estimated to be approximately $21 million and $24 million, respectively, for a total gain of approximately $45 million. The management fees of a single-source solution were 1 to 4 percent higher than those of a multi-source solution. However, these fees are small in comparison to development cost reductions and revenue gains from faster times to market and may be offset by lower sponsor management and legal costs. Any gains from single-source contracting depend positively on the extent to which the development process can be shortened for later clinical testing phases.

Holland New says that, while the savings associated with the single-source solution are higher than Patheon originally anticipated, the value of an end-to-end solution is something the company always understood. This is why the Patheon OneSource™ program is tailored for a seamless coordination between drug substance and drug product manufacturing. "When we launched Patheon OneSource™ two years ago, we knew that streamlining drug substance and drug product would bring obvious efficiency advantages, but we wanted to deliver more than that to clients. We architected the role of the single point-of-contact for the client across the entire Patheon network," she explains. "Then, we added a customized scientific molecule team and project managers for drug substance and drug product. We can't measure the economic returns of proactive problem solving, but it's something that we do for our clients every day."

Conclusion

The pressure of being first to market is compounded by the risks of drug development. Manufacturers invest a considerable amount of resources into a product knowing only about 12 percent of drug candidates are approved by the FDA after Phase 1 testing.[4] They must be able to beat their competitors to market through an efficient execution of the drug development process. Holland New says a single-source solution can play a vital role in meeting these goals. "A single-source CDMO offers small and emerging companies an end-to-end solution with in-house resources that can determine, in real time, how it can scale up and ultimately launch your product. Also, by reducing tech transfers, there is no knowledge lost along the way and you can optimize drug substance and drug product early through one formulation and elimination of duplicate testing." She continues, "The most important driving factor in our industry should be the health of the patient, which is why getting drugs to them faster is a crucial element of what we do."

"A single-source CDMO offers small and emerging companies an end-to-end solution with in-house resources that can determine, in real time, how it can scale up and ultimately launch your product."

Choosing an outsourcing model that provides a market advantage over your competitors is critical, and the Tufts study shows the benefits a single-source solution can offer. It is imperative to select a partner that can also provide the highest level of quality, right-first-time (RFT), and customer satisfaction. It is these qualities that will successfully guide your product through this high-stakes race to market and deliver on the industry's commitment to improving patient health.

1 Tufts CSDD, Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion — http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

2 Deloitte, 2017 global life sciences outlook— https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2017-life-sciences-outlook.pdf

3 The JAMA Network, Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval — https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2653012

4 PhRMA, 2015 Profile, Biopharmaceutical Research Industry —http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf

Patheon
4815 Emperor Blvd, Suite 110
Durham NC 27703-8470 USA
P: +1 919 226 3200
F: +1 919 474 2269
www.patheon.com

Patheon
Kingfisher Drive
Covingham, Swindon
Wiltshire SN3 5BZ UK
P: +44 1793 524411
F: +44 1793 487053
www.patheon.com

Patheon
7F Wakamatsu Building, 3-3-6
Nihonbashi Hon-cho, Chuo-ku,
Tokyo 103-0023
Japan
P: +81 3 6202 7666
F: +81 3 6202 7676
www.patheon.jp

+1 866 728 4366 • patheon.com • doingbusiness@patheon.com