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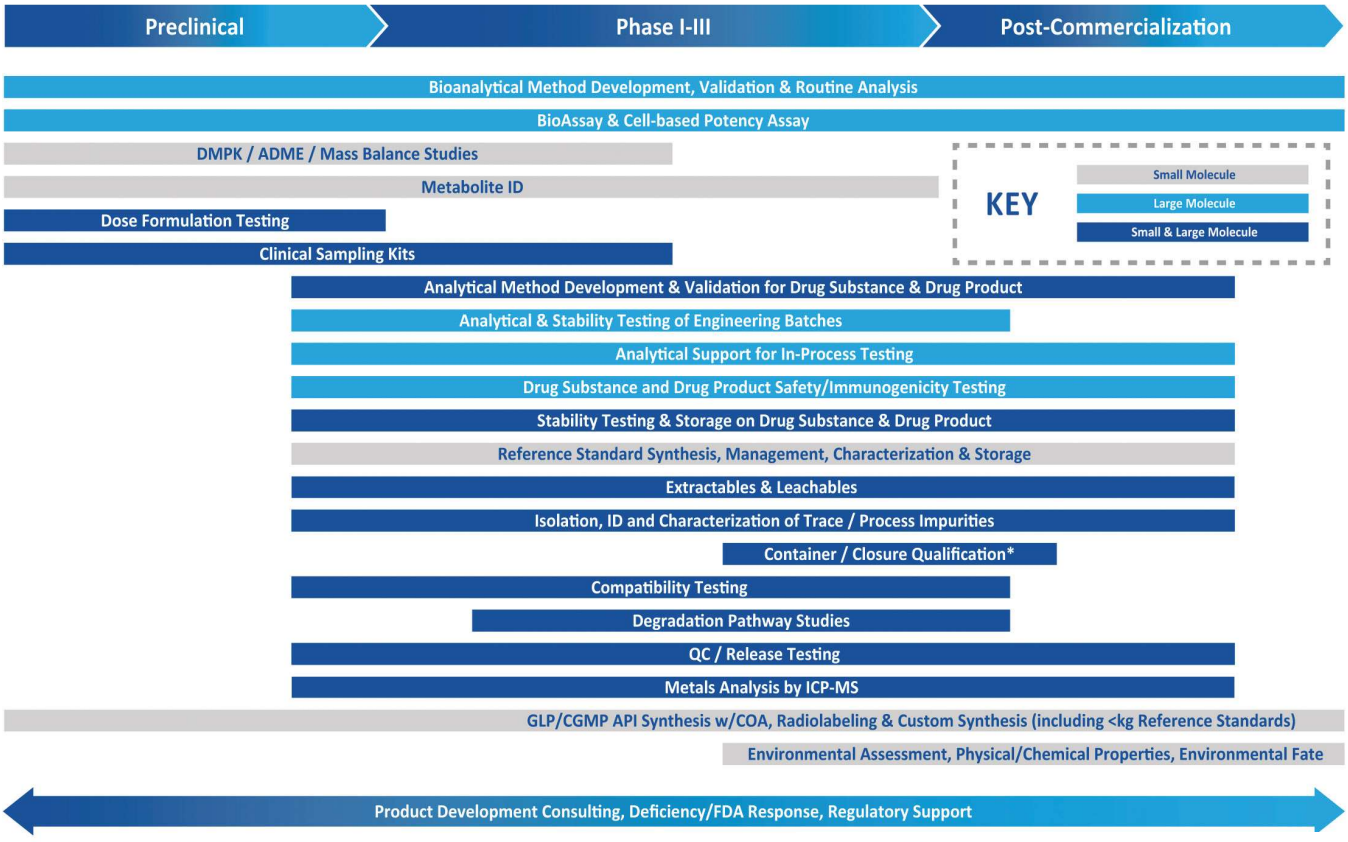

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More Than Rise In Biologics Prompts Reorg At FDA

p. 24

> "The reorg would fulfill a lot of ideas that had been talked about for a long time."
>
> Steven Kozlowski, M.D.
> Director of the FDA's Office of Biotechnology Products

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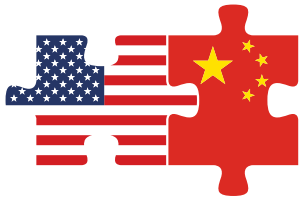

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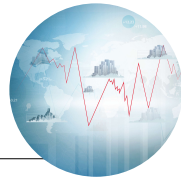

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Kyle Bass – Prophet Or Fear Profiteer?

ROB WRIGHT Chief Editor

This past August, Anna Rose Welch, executive editor of BiosimilarDevelopment.com, wrote an article titled "The IPR Process: How Will Pharma's Patents Fare?" The question was in reference to the recent exploits of Hayman Capital Management hedge fund manager Kyle Bass, who has been using the Inter Partes Review (IPR) proceeding to issue 16 patent challenges held by eight pharmaceutical companies.

The Bass attack of biopharma began with Acorda Therapeutics back in February of this year and was promptly met with a written response from Jim Greenwood, president and CEO of BIO, who stated, "Bass has opened a new door to abuse of the U.S. patent system, exploiting the USPTO's [United States Patent and Trademark Office's] patent challenge proceeding as part of his cynical short-selling strategy against innovative biotech companies that are delivering transformative therapies to patients in need." A March *Bloomberg Business* article followed by an April *Wall Street Journal* piece seem to concur with Greenwood. But, if you think Bass is looking to score a few million by short-selling a few biopharma stocks, you are probably forgetting that he has a tendency to take a rather big-picture approach. To better understand him you need to dig into this profiteer's prophetic philosophy, founded on pessimism, fear, cunning, and a willingness to "hedge" his bets.

In 2007, Bass turned his prediction of the subprime housing mortgage crisis into over half a billion dollars — a rare financial success during what, for most, was a global economic meltdown. In 2012, it is estimated Bass made 650 times his investment on the Greek debt crisis. In other words, Bass bets big. An assessment by patent-focused consultants at Markman Advisors reveals the Kyle Bass pharma patent IPR strategy to be much more sophisticated and long-term than most might think and that any conclusion about his ultimate investment strategy remains a speculation. The most likely scenario seems to be that Bass is preparing to set up the entire branded pharmaceutical industry. A *Business Insider* publication from 2011, "15 Brilliant Insights From Hedge Fund Superstar Kyle Bass," provides the necessary knowledge. Insight number three: Psychology is more important than the quantitative analysis. American citizens are up in arms about high-priced drugs. If you want the masses to rally behind you, align yourself as one of them. Could this be why the IPR petitions filed by Bass have been done on the behalf of the Coalition For Affordable Drugs (ADROCA) LLC?

In a letter dated April 14, 2015, Bass wrote to the chairman of the U.S. House of Representatives Judiciary Committee, Bob Goodlatte, stating that he intended to challenge the existing patents of branded prescription drug companies "in order to police the abusive patent tactics used by the worst offending drug companies." Bass business insight 15: He thinks social unrest will continue to grow. That being said, it never hurts to hedge your bets by fanning the high-priced drug flames via the IPR patent process. In other words, let's not get carried away celebrating the recent IPR wins by Acorda and Biogen. Of the 11 new positions taken by Hayman Capital Management since June 30, 2015, 10 are biopharma and include the likes of branded behemoths (e.g., Pfizer, Merck) and generic giants (e.g., Perrigo, Mylan). Biopharma's battle with Bass has only just begun. L

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Q What is the biggest challenge for biopharma companies in terms of external innovation?

A TO BE SUCCESSFUL, YOU HAVE TO GAIN CONTINUOUS ACCESS TO FUTURE INNOVATION. To do so, you must: (1) Not be locked out of emerging breakthrough innovations by ensuring access to the IP; (2) Leverage open innovation strategies to go beyond traditional licensing/BD; (3) Enhance the connectivity at the right innovation hotspots. It is crucial for companies to have robust engagement strategies, more than just physical presence. This enables them to be part of the local innovation. Further, organizations must embrace a future world of partners who transcend traditional agreements into an open innovation space with no clear boundaries. Another important pillar is the aspect of successfully steering the collaborations and generating value to all parties.

CHANDRA RAMANATHAN, PH.D., M.B.A.
Senior director of innovation strategy and global program head of life sciences external innovation initiatives at Bayer AG

Q What is the best leadership advice you ever received?

A I DON'T KNOW THAT I HAVE RECEIVED SPECIFIC LEADERSHIP ADVICE, but I do have multiple leadership examples. My father instilled in me the value of persistence; if you want something bad enough, go for it. Do not be dissuaded by temporary setbacks, and practice persistence daily. Persistence has helped me in recent years as I have returned to playing piano, something I did as a child and disliked. I love it now, but I must practice for hours to maintain some proficiency. I also pride myself on exploring new ways of doing things. For example, years ago I made a commitment to creating a series of coaching videos. Over the years I have become much more adept with this medium and many have found my videos instructive as well as helpful.

JOHN BALDONI
Chair of the leadership development practice of N2growth, a global leadership consultancy, and author of more than a dozen books, including *MOXIE: The Secret to Bold and Gutsy Leadership.*

Q What is the greatest insight you gained from attending a conference this year?

A WE ATTENDED THE PATIENTS AS PARTNERS IN CLINICAL TRIALS CONFERENCE in March 2015. Presentations discussed specific examples not only of how patient-oriented approaches could be used to promote clinical trial enrollment and retention, but also of how such programs were being used to refine overall approaches to studying and treating disease so as to provide more meaningful results to patients. We brought back and were able to incorporate specific approaches to gathering and utilizing patient feedback about the scientific and logistical aspects of Purdue's protocols, as well as an understanding of key success factors for such programs.

MITCHELL KATZ, PH.D.
Head of medical research and drug safety operations at Purdue Pharma, L.P.

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Mucosis

Needle-free, mucosal vaccines that trigger a two-fisted immune response offer the first hope for fighting RSV – and raising the bar in vax technology.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Mucosis is a Netherlands-based vaccine developer with the proprietary Mimopath platform, which uses bacterium-like particles (BLPs) as a vector for delivering antigens through mucosal tissues, mediating local mucosal and systemic immune responses with needle-free (nasal) vaccines. The company is about to begin a Phase 1 trial with its lead vaccine, SynGEM, for preventing respiratory syncytial virus (RSV) infection.

WHAT'S AT STAKE

Maybe it's the needle — a mass, primordial memory of the sharp, grimace-and-bear-it injection administered by a scary stranger in white, now resurfaced as a generational rebellion against vaccines. Of course, vaccine opponents will scoff at the suggestion, once more citing their redundantly discredited claims of vax-caused diseases; though seen objectively, their blind persistence resembles the kind of tantrum a child might show facing the needle. Opponents have no interest in improving vaccines, of course; they just want to ban them the way Boston banned sexy novels. It is up to vaccine supporters to look honestly at existing challenges for vax technology and find solutions. How about vaccines without needles?

Mucosis believes it has found a way to eliminate needles from most vaccinations and make them more effective as well. Its vaccines enter the body the way 90 percent of pathogens do: through the nose and other mucosal tissue. The "mucosa" also happen to be where the innate immune system lies in wait for invading microbes that display a foreign antigen and, when it detects the invaders, attacks them on-site — while also rousing the adaptive immune system to a systemic response. Thus, by delivering antigens through the mucosa, the Mucosis vaccines elicit not only a systemic immune response but also a mucosal response throughout the body as well.

The company branched out in 2007 from a Dutch government-sponsored research institute, Biomade Technology, based on work by a scientific team at the University of Groningen in northern Holland. "The scientists were looking for ways to more quickly age cheese," relates Tom Johnston, Mucosis CEO. "But what they discovered was the human-grade product of *Lactococcus lactis* bacteria could be wiped clean of any residual components inside and the outer wall of the bacterium would remain. And they took it from there into vaccine research because it would create a particle-like structure and generate an immune response. It is a safe product — we eat it every day in prepared foods, probiotics, and yogurts, but the idea was how it could work with vaccine antigens for mucosal delivery."

After a successful Phase 1-2 proof-of-concept trial in influenza, the company chose to develop its first commercial vaccine for RSV, a serious crippler of infants and elders. No RSV vaccines currently exist, although a handful of companies is working on them, including Johnston's former employer and reputed pack leader, Novavax. "We think that we have a better mousetrap for a number of reasons, and we're right behind them and nipping at their heels," he says.

The real stakes: Johnston emphasizes that RSV is often confused with the flu, but in the elderly, the virus can cause death or comorbidity, and in infants, especially those born early, it can cause life-long bronchitis, asthma, or other lifetime illnesses. "By the age of two, everyone has had RSV," he says. "But you can be re-infected year after year, even though the virus hasn't changed."

TOM JOHNSTON
CEO

Vital Statistics

12
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Headquarters
The Netherlands

Finances

Total raised:
€20M+
Private company

Lead institutional investors:
BCHT - China; and MedSciences Capital, BioGeneration Ventures B.V., NV NOM, UU Holdings – Netherlands

Research partnership funding

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May 2014
Netherlands Enterprise Agency – Up to €5M

Other partners (vaccine research)

Department of Virology, University of Utrecht (RSV)

PATH (USA, Shigella/ETEC)

Laboratory for Pediatric Infectious Diseases, Radboud University Nijmegen Medical Centre (pneumococcal bacteria)

Center for Vaccine Development at the University of Maryland (pediatrics)


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Recognizing Abuses, HRSA Issues Draft Guidance On 340B

JOHN McMANUS The McManus Group

It took a series of damning government reports and investigations documenting the growing abuse of the 340B discount program by nonprofit hospitals and generally lax oversight by the Health Resources Services Administration (HRSA) that administers the program to finally prompt the agency to issue new guidance on how those covered hospitals should operate under the program.

- A 2011 Government Accountability Office (GAO) report found that HRSA had scarcely conducted an audit of a covered hospital and relied almost entirely on "self-policing."
- A 2014 HHS Office of Inspector General report found that 340B hospitals' use of contract pharmacies ballooned by 1,245 percent and presented "complications" regarding drug diversion and duplicate discounts.
- A 2015 GAO study showed drug spending for 340B hospitals was twice that of Medicare Part B outpatient spending per beneficiary because of incentives to prescribe more and expensive drugs.
- An investigation by Senator Charles Grassley (R-IA) found that many 340B hospitals' profits from charging their patients substantially more than the discounted prices they acquired the drugs for greatly exceeded the charity care they provided.
- A June 2015 Medicare Payment Advisory Commission report showed 340B-covered entities and their affiliates spent over $7 billion to purchase 340B drugs in 2013 — three times the amount spent in 2005 — and suggested that Medicare should benefit from the steep discounts 340B hospitals were reaping.

Congress enacted the 340B drug discount program in 1992 and substantially expanded its scope in the Affordable Care Act in 2010. The program now enables more than one-third of hospitals to obtain substantially discounted outpatient drugs for all their patients (except Medicaid) — whether they are uninsured or covered by Medicare or a commercial insurer. The discount is tied to the Medicaid rebate percentage, so many drugs are discounted at 40 to 50 percent or more, and the hospitals can reap a profit by providing them to Medicare and commercially insured and even uninsured patients at market rates.

A September 2015 study by the Berkeley Research Group found that 340B hospitals realized a 123 percent increase in Part B reimbursement for oncology drugs between 2010 and 2013 compared to just 31 percent for non-340B hospitals, while reimbursement in physician offices for the same drugs declined by 5 percent. The 340B program has been a major catalyst in the hospital acquisition of physician practices. Berkeley also found that 340B hospitals receive 50 percent more Part B drug reimbursement per beneficiary than community oncology practices.

Originally intended as an omnibus "Mega-Reg," successful litigation by PhRMA preventing the applicability of the program to off-label uses of orphan drugs circumscribed the agency's rulemaking ability and forced HRSA to issue interpretive guidance instead. That guidance was issued on Aug. 28 and solicits comments from affected stakeholders, and the white-shoe law firms that advise both the pharmaceutical and hospital industries are hard at work poring over the text and fashioning responses. The comment period is open until Oct. 27, after which HRSA may elect to publish the changes or subject them to further revision.

THE NEED FOR GREATER OVERSIGHT

While many in the pharmaceutical industry felt the guidance did not go far enough, it clearly validated the fundamental tenet that the 340B program's abuses had become excessive and that the hospitals benefiting from the program require greater oversight and policing. For example, it creates a new six-part test to determine whether an individual receiving a discounted drug is actually an eligible "patient." The guidance provides a new requirement that the prescribing physician be an employee or have a contract with a 340B-covered entity. In addition, the determination is made on a prescription-by-prescription basis,

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meaning the patient must be re-evaluated for eligibility each time. The patient can be prescribed a drug only if admitted as an outpatient. And importantly, hospital employees are specifically excluded from 340B-priced drugs unless they are also patients of 340B-covered entities — an important victory because many 340B hospitals are actually part of sprawling university campuses, like Duke University and Johns Hopkins University, that employ entire communities.

The guidance also provides a new auditing and enforcement capability, including annual certification of covered entities and its "child sites," the off-campus outpatient facilities owned by the hospital and eligible for 340B discounts. Records and documentation must be retained to validate eligible patients. 340B hospitals have total responsibility for contract pharmacies' adherence, and annual audits of those pharmacies are suggested.

Notwithstanding these improvements, the pharmaceutical industry has expressed dissatisfaction with the guidance because it fails to curtail the number of contract pharmacies. The number of 340B-covered entities contracting with retail pharmacies and mail order/specialty pharmacies has soared to over 3,000 this year from less than 1,000 in 2010, according to the Berkeley report. The proliferation of contract pharmacies in 340B presents serious potential for drug diversion since the patients are not receiving the drugs at the hospital. Moreover, it's hard to understand why exponential growth in contracting of chain drugstores in affluent areas is needed to service indigent hospital patients. The attraction of marking up and profiteering from discounted drugs is clearly substantial.

The pharmaceutical industry is also concerned that a terminated 340B hospital — presumably for flagrantly violating new terms of the program — can re-enroll the next year. These hospitals simply need to repay manufacturers for discounted drugs it was not entitled to and demonstrate a commitment to abide by the statutory requirements.

But hospitals complain that the reforms are too onerous and undermine their ability to serve patients. Beth Feldpush, senior vice president of policy and advocacy at America's Essential Hospitals, grumbled that the audit trail that would be required to demonstrate that the right prescriptions were discounted may encourage some hospitals to abandon the program. "It's one thing for the pharmacist to be able to look up the patients' insurance status and another thing for the pharmacist to ensure each prescription meets the new multipoint test in the guidance, which demands information the pharmacist likely wouldn't have," she said.

But it is important to recognize this proposed guidance as noteworthy because it begins to halt the Obama administration's own overreach and fixation with transferring resources from the pharmaceutical industry to other "deserving" actors, in this case, largely urban hospitals. Liberal groups are scratching their heads because a major strategy for funding Obamacare was through Medicare cuts to hospitals, which would surreptitiously be kept whole through enhanced resources from the pharmaceutical industry by expanding the scope and impact of the 340B program.

In any case, the proposed guidance should be seen as a first step toward reforming the program. Since it is only guidance and not a rule, it's unclear whether the modest, suggested reforms are enforceable. More importantly, it does not go far enough because it can only interpret the current law. New legislation is needed to fundamentally reform the 340B program, and that must come from Congress.

There was a flurry of activity regarding 340B reforms in the final stages of House consideration of the Energy & Commerce Committee's 21st Century Cures legislation at the end of the summer, and the pending guidance actually hampered a legislative solution because both sides were eager to see how HRSA would retool the program. But consensus could not be achieved in that compressed time frame, as the Energy & Commerce Committee chairman was focused on enacting the omnibus package before the August Congressional recess.

"New legislation is needed to fundamentally reform the 340B program, and that must come from Congress."

Perhaps the issuance of the proposed guidance and increased focus on the program can encourage the political parties to come together and develop a proposal that returns 340B to its original mission of assisting the uninsured and indigent, not sprawling mega-hospitals and chain drugstores.

The political stakes are high. 340B hospitals are well organized and reside in almost every member's district. Pharmaceutical companies are confined to a few zip codes but are armed with a growing stack of government-sponsored studies documenting increasing abuse of the program that the administering agency now explicitly recognizes. L

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

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Do Outcomes Matter When There Is Chronic Misalignment?

ALLAN L. SHAW

"It is ironic that a longstanding fringe benefit such as medical insurance could actually serve as an antithesis to an optimal patient care system focused on outcomes and system savings."

With over $3 trillion in annual healthcare spending, a relatively young population, and shorter life expectancies than other western nations, one would think there would be vast opportunities for the U.S. healthcare industry to rein in costs, weed out inefficiency, and improve outcomes. Instead of yielding to "regression toward the mean," however, the highest global per capita healthcare machine marches to 20 percent of total GDP. Unfortunately, reform is much easier said than done considering the number of factors and stakeholders that make up our complicated and varied healthcare landscape. The various operating segments within the health sector have traditionally made decisions according to their own business priorities, a silo mentality which propagates vast wastefulness and poor care coordination. This systemic misalignment is further compounded by stakeholders who are often focused on short-term cost and profit as opposed to outcomes (system value). The lack of correlation (accountability) between spending and outcomes in the face of global cost containment initiatives reflects the imperative to change the economic/reimbursement model and shift emphasis from quantity to quality. This paradigm shift, which has already been bought into by Medicare, Medicaid, and commercial ACOs (accountable care organizations) will require openness to new forms of business harmonization and alignment of the various stakeholder perspectives to coexist and, more importantly, ensure a successful transition to a value-based reimbursement system.

In the backdrop of this healthcare industry renaissance, U.S. drug spending experienced the highest level of growth in nearly 15 years, which was driven by new and exciting specialty drugs in therapeutic areas such as hepatitis C, oncology, and MS (e.g., Solvadi/Harvoni, Keytruda, Yervoy/Opdivo, Tecfidera). Specialty medicines have become a lightning rod for drug pricing, representing a growing one-third of total drug spend. This generates fear that the cost of these specialty drugs will break healthcare budgets and make these drugs the poster children for curbing healthcare costs.

Additionally, the growing cost of specialty medicines is sparking a marketing and policy battle between the pharmaceutical industry and healthcare plans that cover those drugs. There is an increased focus on pharmacoeconomics (used by purchasers in deciding which drugs to cover) as well as on price as a key component of a drug's expected health benefit. This price emphasis has exposed significant structural misalignment in the healthcare ecosystem that, if not addressed, will not only impede stakeholder alignment but also will marginalize the importance of outcomes, particularly in chronic care settings.

THE NEED FOR A FOCUS ON CHRONIC DISEASES

The healthcare system's approach to chronic disease epitomizes all that is wrong with the current system and highlights the need for structural change in disease and patient management among stakeholders. Given that chronic conditions represent 86 percent of total healthcare spend and that approximately 30 percent of patients have multiple chronic conditions, there must be a shift toward chronic care and away from acute treatment. This also reflects the overriding need for a holistic, outcomes-driven strategy to manage chronic disease.

The recent Sovaldi/Harvoni pricing debate (originally listed for $84K before decreasing in price by nearly 50 percent due to competitive pressure from an arguably a less-effective product) highlights this chronic disease schism. Sovaldi has led a revolution in the oral treatment of hep C and revealed the significant lack of alignment on a number of fundamental points impacting optimal treatment for chronic diseases. Perhaps the most salient revelation is the fundamental disconnect with employee-provided healthcare benefits.

Managed care underwrites risk that generally correlates with employment tenure patterns (e.g., three to five years). Unfortunately, these time horizons are completely disjointed from chronic

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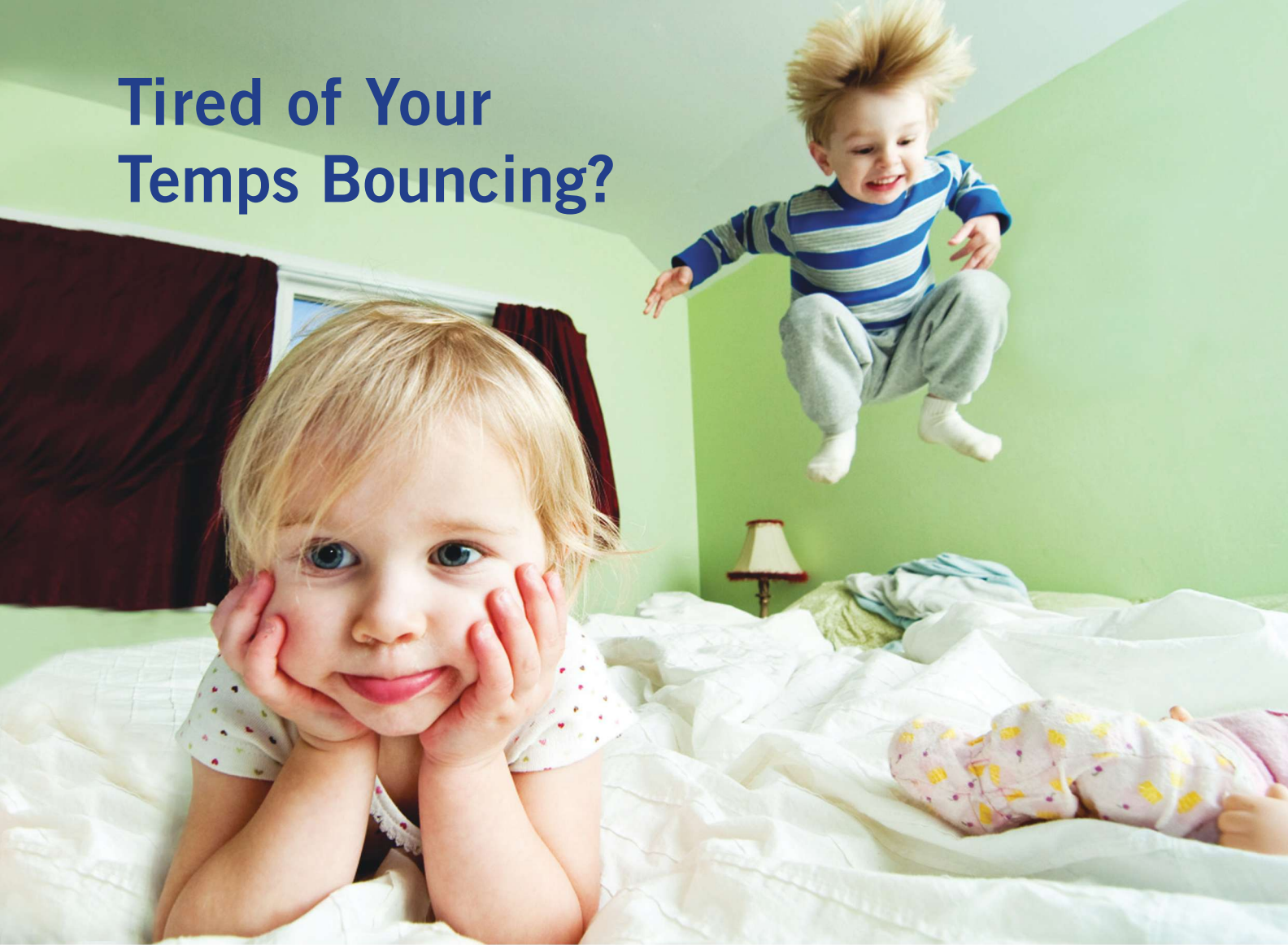

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illness, reflecting the inherent incompatibility with managed care's fiscal objectives and the need to provide optimal patient care, or in the case of hep C, a cure for a debilitating chronic disease. For example, why would managed care want to pay for Solvadi to cure a patient, thereby avoiding a liver transplant in 20 years and saving millions of dollars, when those benefits will likely not accrue to them? Given that insurance companies don't want to pay more money, managed care might argue that it is in its interests to let Medicare pay for the expensive innovative treatment after patients turn 65. From a purely business perspective, it is easy to understand why managed care organizations are taking on characteristics of our government and simply kicking the can. This dynamic underscores the concerns that the healthcare system, as presently configured, will not be able to support widespread access to innovative medicines that improve outcomes.

It is ironic that a longstanding fringe benefit such as medical insurance could actually serve as an antithesis to an optimal patient care system focused on outcomes and system savings. This disconnect requires structural reform to facilitate a homogeneous risk pool to align cost-effective patient outcomes with financial incentives (e.g., risk sharing) that benefit all stakeholders. In my view, employee health benefits as we know them will ultimately go the way of the dinosaur, supplanted by the healthcare exchanges, very much akin to our migration from defined benefit plans to defined contribution plans. It should be noted that the Affordable Care Act (ACA) foresaw this inevitability and has provided employers with incentives to facilitate this migration. Furthermore, this evolution also would alleviate ongoing changes in insurance designs and the consequential fragmentation of care patterns that can often disrupt medication adherence and put patients at risk.

ACCOUNTABILITY HAS TO INCREASE

Indeed, behaviors within our current health system must change to ensure that outcomes really matter. Perhaps with structural reform, pharmacy benefit managers (PBMs) will switch from focusing on minimizing current-period costs to emphasizing outcomes and enabling overall healthcare system savings. Until such changes are implemented, optimal patient access to innovative products for other chronic indications will be challenging due to the lack of accountability concerning medical spending and health outcomes. For example, with PCSK9 inhibitor therapies that are designed to reduce cholesterol, the jury is still out on their cost-effectiveness since their value will ultimately depend on their ability to fulfill their promise of lowering mortality and/or clinical cardiac events in large scale trials. These studies will not only illustrate the cost-effectiveness of innovative therapies like PCSK9, but they also will help maximize the commercial value of these products, facilitate patient access to innovative medicines, and foster alignment among stakeholders.

Unfortunately, putting drug costs into context will require many things such as:

- capturing and measuring outcome data to understand its clinical and economic impact. This is fundamental to demonstrating and enabling risk sharing, particularly in an environment where the stakes are high and there is a lack of trust.
  - There will be an ongoing need to measure patient outcomes after a drug receives FDA approval to quantify its pharmacoeconomic impact on the healthcare system.
  - More collaboration and partnerships will be needed to facilitate access to patient data and evidence that connects drug intervention to cost-effective outcomes.
- establishing objective, standard definitions and quality measures that drive value. For instance, I do not believe a standard definition for quality exists.
  - Patient rehospitalization rates provide a good example of a quality measure, particularly given the high level of readmittance (e.g., 20 percent readmitted within 30 days, and 60 percent are readmitted within 60 days). Simply put, demonstrating a reduction in rehospitalization would highlight a drug's value while eliminating wasteful healthcare spending; for example, ACA reforms already include penalties for heart failure patients who are readmitted for heart failure to the hospital within 30 days of discharge.
- improving patient compliance by establishing support programs and optimizing administration. Patient noncompliance diminishes the value of biopharmaceutical products. It also reflects a growing concern that drug development doesn't adequately address patient needs and medication adherence outside of the clinic, underscoring the call for real-world outcome data.

There is no denying it — change is inevitable and must be embraced. Optimal patient outcomes must be the overarching goal as we seek compromise and alignment with stakeholders. This shared vision is a prerequisite to optimizing patient access and improving the quality of care while reducing overall system costs, irrespective of whether it is an acute or chronic disease. L

ALLAN L. SHAW is currently a member of Akari Therapeutics' board of directors and serves as chairman of the audit committee. He is also a member of the board at VIVUS, Inc. He was recently managing director – life science practice leader for Alvarez & Marsal's Healthcare Industry Group and formerly CFO of Serono, possessing more than 20 years of corporate governance and executive/financial management experience.

A Look At 2015 Outsourcing Trends And What To Expect In 2016

This has been another exciting year in outsourcing, as mergers, acquisitions, and other collaborations continued with CROs and CMOs moving toward functioning as strategic partners.

NIGEL WALKER
Managing Director
at That's Nice

"Personalized medicine and advances in cell and gene therapy also require new research and manufacturing services."

Indeed, while the concept has been around for some time now, the reference to contract development and manufacturing organizations (CDMOs) is more prevalent when it comes to defining the strategic partner approach. The continued expansion of organizations such as Patheon speaks to the trend.

There has been further consolidation with CROs as well, with LabCorp's acquisition of Covance and Chiltern's acquisition of Theorem Clinical Research. Similarly, Big Pharma companies look toward global CROs to share operational practices. It will be interesting to see whether these consolidated companies, both CROs and CDMOs, are able to fully integrate their services and improve their performance.

According to the Nice Insight report on 2015 outsourcing trends, this year saw another big jump in expenditure for CROs and CMOs, maintaining the continuously escalating outsourcing spend over the past four years. Nearly two-thirds (62 percent) of survey respondents from pharmaceutical and biotech companies spent $10 million to $50 million USD in 2014-2015 for outsourcing, a jump of 24 percent from last year and double the number of companies who spent this amount in 2011-2012. Significantly fewer companies (16 percent) spent less than $10 million, a drop from 29 percent last year and 43 percent in 2011-2012 (Figure 1).

The demands from industry service providers have never been greater. Some key trends driving the continuously rising outsourcing budgets include a growing pipeline of biologics, complex therapies and delivery systems, and precision-based medicines, as well as larger, more complex clinical trials, real-world evidence studies, and the need for sophisticated new technologies, all of which require advanced, integrated expertise. Health-economics and outcomes research and data analytics services are also in demand. Biopharmaceutical and biologics companies are increasingly turning to service providers for all aspects of drug development, partly to avoid the very high capital expenditure and long lead times needed to construct, equip, and validate manufacturing facilities.

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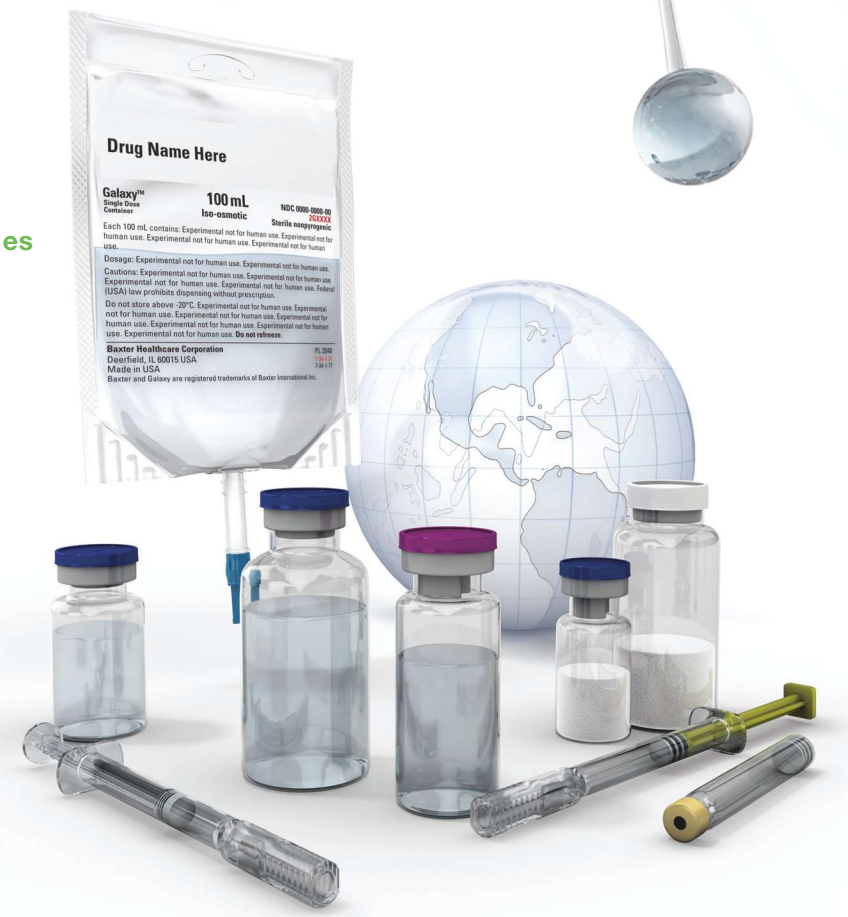

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regulatory pressures on drug manufacturers continuing to increase, it is not surprising that growth of the global CRO and CMO market is healthy at 9 percent and 6.4 percent CAGR, respectively. The globalization of clinical trials also reflects the growth of healthcare and drugs that treat acute conditions for unique patient populations (e.g., orphan drugs). Personalized medicine and advances in cell and gene therapy also require new research and manufacturing services.

The continued increase in expenditures coincides with a decrease in the prioritization of affordability as one of the drivers for selecting an outsourcing partner. While quality and reliability remain the leading factors influencing the choice of partner, regulatory compliance was less important this year, dropping to the bottom of the qualification list of six factors and tied in ranking with innovation (Figure 2). Other considerations include technical capabilities and on-time delivery.

As for the number of services outsourced by company type, Nice Insight research data showed that the average number of services outsourced has increased across the board (Figure 3).

If you want to learn more about Nice Insight, the report, or about how to participate, please contact Nigel Walker by sending an email to nigel@thatsnice.com.

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

FIGURE 1 Annual Outsourcing Expenditure (%)

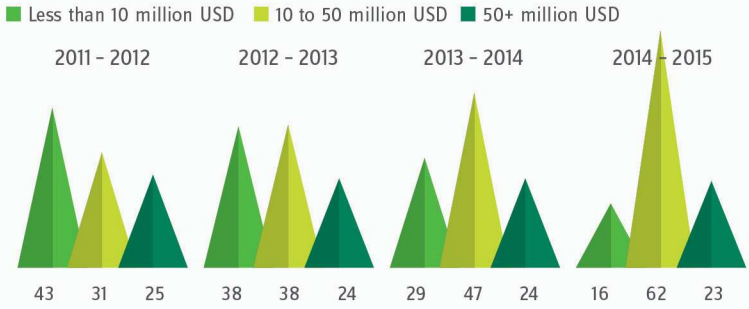
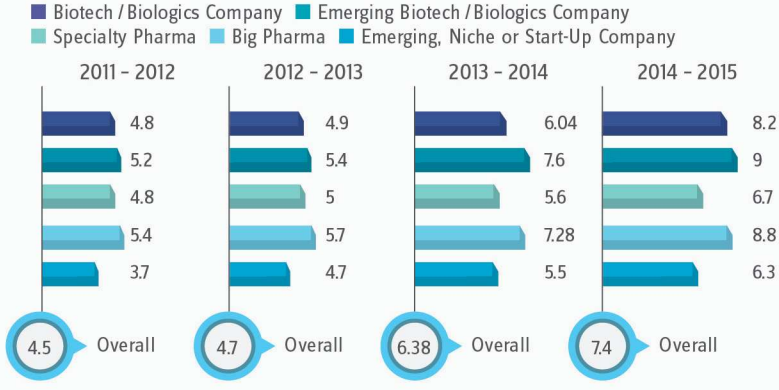


FIGURE 2 Rank of Industry Drivers

	2011 - 2012	2012 - 2013	2013 - 2014	2014 - 2015
Quality	1	1	1	1
Reliability	2	2	2	2
Affordability	3	4	5	4
Productivity	4	5	4	3
Regulatory	5	3	3	5
Innovation*	6	6	6	5

*Accessability in 2011-2012

FIGURE 3 Average Number of Services Outsourced by Company Type



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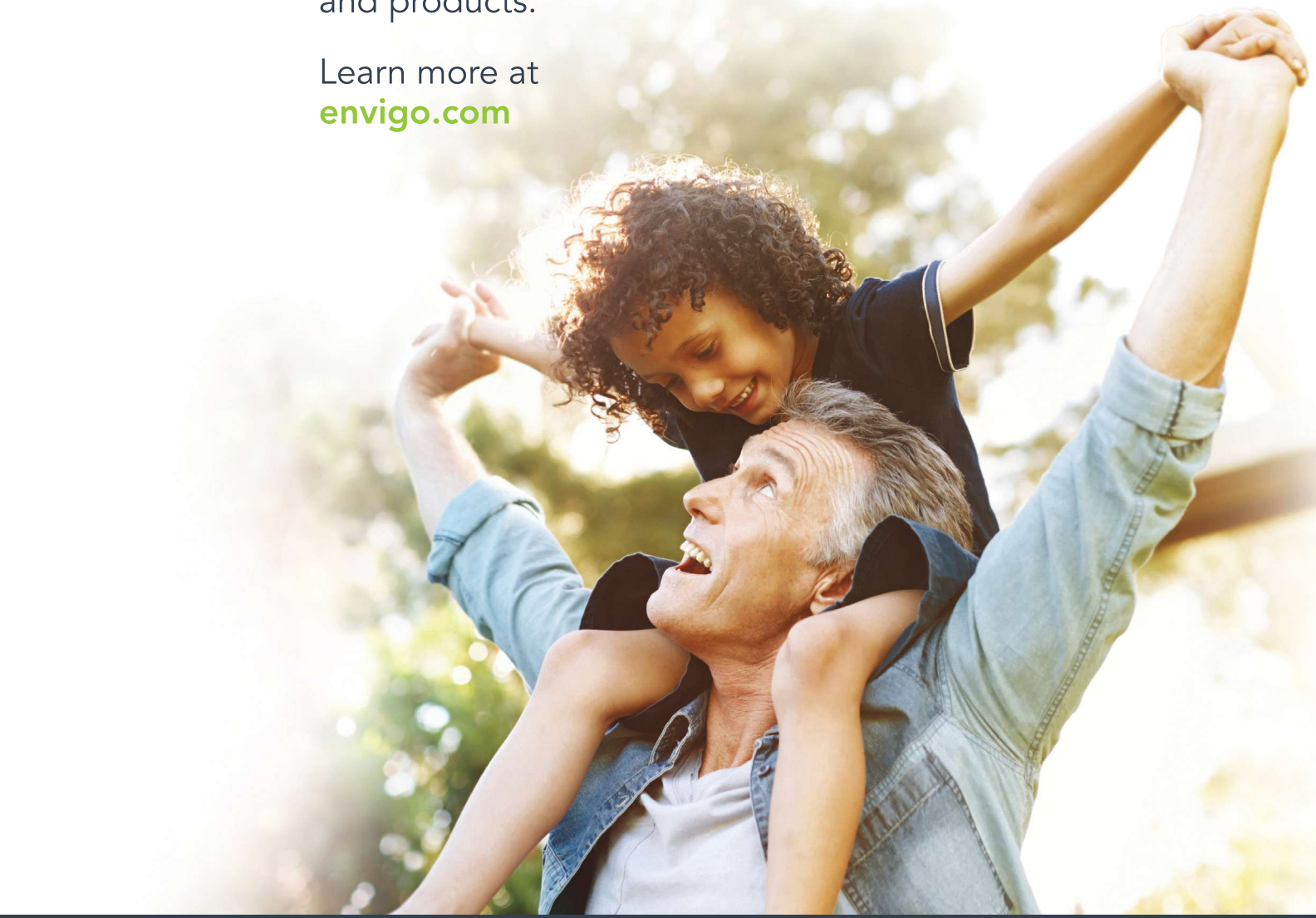

MORE THAN THE RISE IN BIOLOGICS PROMPTS REORG AT FDA | By R. Wright

MORE THAN THE RISE IN BIOLOGICS PROMPTS REORG AT FDA

ROB WRIGHT Chief Editor @RFWrightLSL

"Change is very, very difficult to do in government," says Steven Kozlowski, M.D. In 2012, the director of the FDA's Office of Biotechnology Products (OBP) learned that the Center for Drug Evaluation and Research (CDER) would soon undertake a major restructuring. CDER had decided to reorganize around drug quality manufacturing, potentially including biologics. The plan would really change the Office of Pharmaceutical Science into the Office of Pharmaceutical Quality, and it would focus on greater integration between review and inspection to achieve better manufacturing consistency. "The reorg would fulfill a lot of ideas that had been talked about for a long time, like GMP [good manufacturing practice] for the 21st century, quality by design [QbD], and a whole variety of advanced manufacturing topics," explains Kozlowski. "But there were questions about where OBP, the office responsible for reviewing the manufacture of all biologics in CDER, would fit into the plan [i.e., would OBP be integrated into this new system or be treated differently?]." For example, biosimilars were on the rise, so it would be beneficial to keep a group capable of dealing with the anticipated surge of biosimilars submissions intact.

Eventually the decision was made to leave OBP pretty much untouched. You probably wouldn't be surprised to learn that for many OBP employees the notion of being able to continue "business as usual" was welcome news — at least initially. "A lot of people don't like change," Kozlowski affirms. "But a number of people both inside and outside of OBP approached me saying, 'If a lot is changing within CDER, by doing nothing are we losing an opportunity to participate in a change that will better prepare us to do our job?'" he states. "That question was the aha moment for me."

Despite OBP not being part of CDER's formal reorganizational plans, Dr. Kozlowski did what many government critics might consider unthinkable — he seized the opportunity to implement change when not mandated to do so.

IS THE BIOLOGIC SUBMISSION BUBBLE ABOUT TO BURST?

The decision to make a change had a lot to do with an analysis of current market trends for biologics. "In 2014, we had a little more than 170 original INDs [investigational new drugs]," Kozlowski shares. "Not all of those necessarily had full manufacturing review, which is our primary responsibility." The OBP director estimates there are presently more than 1,300 active biologic INDs within the FDA. The number of biologics being approved isn't nearly as large as that of pharmaceuticals — yet. "I think we had 11 approvals in 2014, but that number doubles every 10 years or so. In the 1980s, there were only about two a year. In 2000 it doubled to about four a year. Since 2010, it's been about eight a year." Considering this trend, combined with the Biologics Price Competition and Innovation Act (2009) moving some additional products into being regulated as biologics, Kozlowski expects another doubling — soon. "Predicting biologics growth is very tricky," he admits. "I estimate it is actually going to grow faster than the current rate." Why? He says there will be continued growth in novel products, the primary contributor to the biologics doubling trends, on top of which you will also have an increase in biosimilars and perhaps the continued rapid growth of antibodies. "If you look at antibodies as a subset of biologics, I think we have close to 60 marketed products," he estimates. "Whether they are antibodies or antibody fusion proteins, there are a lot of INDs for them, and that subset may grow fast for a while, too."

The predominance of antibodies in the biologics space is one reason why OBP, prior to the recent reorganization, used to consist of just two divisions

> *"Predicting biologics growth is very tricky. I estimate it is actually going to grow faster than the current rate."*
>
> **STEVEN KOZLOWSKI, M.D.**
> Director of the FDA's Office of Biotechnology Products

Don't Let Team Identity Become An Unanticipated Crisis

Steven Kozlowski, M.D., director of the Office of Biotechnology Products (OBP), says he and his leadership team had a lot of discussion on preparing for the eventual transition during the recently executed reorganization. In fact, they even distributed copies of the book, *Managing Transitions* by William Bridges, to members of the transition team to help them prepare for possible resistance. "One unforeseen outcome of the announcement of the reorg was that some employees felt they were losing their professional identity. For example, in the old division of monoclonal antibodies, the people there really identified themselves as being the antibody experts. But in the reorg, there would be antibody experts in multiple groups. In these kinds of situations, Kozlowski explained to the staff that they were victims of their own success. "Because the roles you played in helping facilitate these products made them grow so much that the system of doing this all in one division really won't work anymore is a testament to your success." In addition, he informed them that although their organization is losing its identity in the reorganization, OBP would still be tracking their individual expertise. "If you're an expert in antibodies, for example, you're still an expert in antibodies even if you work in a division that doesn't have antibodies as its specific designation," he explained. "Thinking about people's identity issues and managing those issues is just as important as determining whom they're going to work for and where their office is going to be," he concludes.

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The Importance Of Transition Teams And Working Groups

"During a lot of the early parts where we were figuring out how to move people around and setting up a work structure for the eventual reorganization, the transition team was pretty much the current management," says Steven Kozlowski, M.D. But the director of the Office of Biotechnology Products (OBP) at the FDA notes that as OBP got closer to the reorg actually happening, they took the opportunity to create a more rounded transition team. The original team included himself, his deputy director, Jeff Baker, Ph.D., and two current division directors. "But then we did interviews and actually had a selection process to add other people to that group," he states. The goal was to make the process as transparent as possible. Eventually the group grew to nine members. "We thought it very important to have a strong cadre of appropriate leadership during the time of transition," Kozlowski acknowledges.

It was this group that decided who the new acting division directors would be, as well as who would be acting review chiefs — a position that manages the full-time reviewers within the division. The transition team also played a critical role in determining what working groups were needed.

"Before the reorg, we had something called team leader lab chief meetings," Kozlowski says. "If we felt there was an issue that was treated somewhat differently, technically, in one group than another group — say viral clearance for early studies of these products — we would discuss it there, and we would try to figure out whether the difference was based on a true technical scientific reason or whether we should try to be more consistent in how we approach that across the organization."

While these meetings remain important and still occur weekly, the transition team realized there had to be a better way to share knowledge and best practices across four divisions that could potentially be reviewing the same type of product. The result was the creation of dedicated working groups that included representatives from all four divisions. These groups, often consisting of between eight to 10 people, tend to meet weekly, but the frequency can vary. "We have a working group for biosimilars, so that we can make sure we're treating biosimilars in a consistent manner across the office, because there potentially could be two biosimilars to the same reference product being reviewed in two different divisions," he explains. This can also occur with novel biological products. For example, on Aug. 27, 2015, the FDA approved evolocumab as an antibody to the target PCSK9 gene. Another antibody to the same target, alirocumab, was approved in late July 2015. "These two products, both monoclonal antibodies against the same target, were reviewed in two different divisions by two different teams," Kozlowski explains. And while he views this as a demonstration that the reorganization is working, he also feels this exemplifies how working groups help to ensure consistency across OBP's four new divisions. "We have a working group for immunogenicity, because again, while immunogenicity may be a different risk based on the nature of the product, it's very important to have consistent ways of looking at that across the office," he states. "Even though the adverse events for immunogenicity are a clinical issue, we play a large role in reviewing the assays for immunogenicity and important interactions to help determine if there is a link to adverse events."

Working groups play a critical role in OBP's strategy of having any division review any product. In fact, Kozlowski says they will be constantly re-evaluating whether additional working groups are needed.

organized around product structure. "You know, one for antibodies and one for everything else," Kozlowski laughs. This structure may have made sense when OBP was part of the Center for Biologics Evaluation and Research (CBER) or even in the early 2000s when it was first moved to CDER. "The growth of antibodies created some unevenness within OBP," he says. "It's hard to predict what'll be hitting our desks over the next 5 to 10 years. Although we know antibodies are growing, we really don't know by how much and what percentage of IND applications they will represent or even whether there'll be some new thing to consider."

Once the decision was made to reorganize, the first challenge facing Kozlowski and his team at OBP was what structure the new organization should take. "If you try to reorganize while trying to be prophetic about what will happen in the future, if your industry and marketplace predictions aren't accurate, you will just end up needing to reorg again," he explains. This was something he was hoping to avoid.

GROWING FROM TWO TO FOUR DIVISIONS

One of the first issues that had to be resolved was how the workload would be best managed.

"We were operating with 50 to 60 FTEs [full-time equivalents per division], which is a large number of people for someone to manage," says Kozlowski. His initial idea was to just add another division, which he discussed with some of the managers involved and also with the managers in OPQ (the Office of Pharmaceutical Quality), under which OBP resides within

CDER. The consensus was that just adding another division would be too short-sighted. "If we were at capacity when we started, we haven't really achieved much," he concedes. "That drove the idea of creating four divisions, with each being small enough to be managed effectively but still having the ability to grow a little." As a result, four new divisions of biological product review and research (DBRR) were created and simply named DBRR 1, 2, 3, and 4.

The next step was to determine how to divide the work. "That process involved a massive number of pie charts," Kozlowski shares. "We realized we needed other ways of dividing product classes." In the past, for example, when the antibody load became too high for the antibody division, IND products that consisted of fusion proteins were shared with the other division. Kozlowski says they considered an option that included continuing to divide antibodies in this manner while also dividing enzymes separately from cytokines. In fact, they considered multiple options and configurations — a process Kozlowski describes as almost an exercise in futility. "You could divide this work in a variety of ways, each of which makes sense on its own right now, but you would likely be constantly tweaking the number of divisions depending upon what's dominant in the marketplace in the future." Ultimately, they decided on divisions that review therapeutic proteins, whether antibodies or not.

This idea of having four divisions within OBP that didn't have specific areas of expertise got a lot of pushback. Kozlowski says some of the questions surrounding this decision included, "How would we assign work, then? How would we maintain expertise? How would we ensure consistency in four groups where everybody does everything?" In order for this new noncategorized division system to work, OBP would need some means to control assignments centrally.

AN ALGORITHM TO MATCH EXPERTISE TO PROJECTS

As part of the reorg at OBP, there existed a group of individuals acting as project managers. "These people were managing review assignments," Kozlowski says. "Life cycle products tended to go to the group that previously reviewed them to ensure continuity." This was fairly straightforward. However, when it came to assigning new work, the challenge was to make sure you had the right type of expertise for each assignment. "That led to the idea of what we're calling 'the algorithm.'"

Serendipity Plays Role In Removing Silos

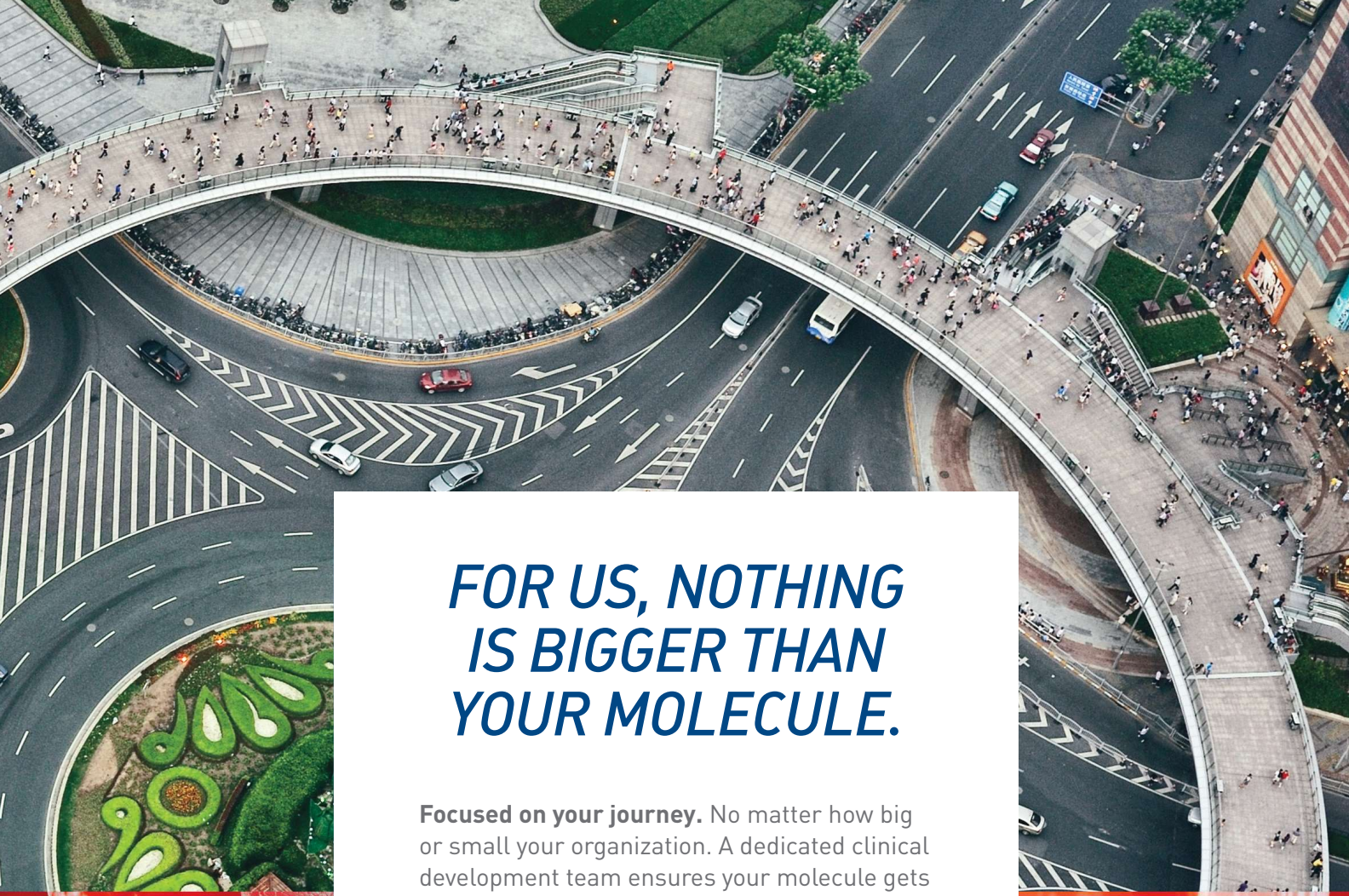
During the process of reorganizing the Office of Biotechnology Products, its director, Steven Kozlowski, M.D., was faced with another big move, one that was actually a physical relocation. "The vast majority of OBP was located at the NIH, including our laboratory program, which is a very large and complicated effort," he explains. The plan was to relocate OBP from the NIH Bethesda, M.D., location to the FDA's White Oak campus in Silver Spring, M.D.. Though only a 25-minute move, Kozlowski says if you think moving people around is hard, moving labs is harder. "This led to a whole bunch of interesting challenges," he shares. "We're reorganizing. We have an idea about what the new divisions will consist of, but because of the way the rules work, we can't really share the final org charts until they get approved. How do we move people into new offices when we can't necessarily share what division they're going to be in?"

For Kozlowski, this challenge turned out to be a bit of serendipity and an opportunity that fit nicely with the goal of OBP being less siloed. Here's why: The reorganization of OBP was more a mental exercise that began in early 2013. "We had our idea of how 150 people would move during the crosswalk [a term used by government to denote the implementation of the reorganization] in early 2014," he shares. "But the actual reorg didn't happen until Jan. 15, 2015." However, the physical move required a much more rigid timetable in order to be successfully executed during the summer of 2014. "We were all so busy with the physical move that while we were waiting to get the reorganization approved, people had a lot of other things to worry about beyond what division they would be in," he notes. "Besides, why do we really need to keep divisions physically together anyway? If all the divisions can review similar products, maybe having your next-door neighbor being from another division where you talk to them and ask questions is actually a good thing." Although he admits it was challenging to have all of these things going on at once, it turned out to be a real benefit. "Working together on one campus in a way that we weren't before reinforced the idea of being part of one connected office," he states. Kozlowski believes that everybody mixed together will be much more important to building a cohesive culture at OBP than relying on lines drawn on a formal organizational chart.

Basically, the algorithm starts by looking at workload, which is scored based on weighing different kinds of assignments, INDs, and manufacturing supplements. The algorithm also looks at experience. "It's a management-based ranking of experience," Kozlowski confirms. "We ask questions such as, 'Does this person have experience in this area? Have they reviewed a lot of antibodies? Have they reviewed a lot of enzymes?'" Management created a simple scoring system to rate that experience as one factor in the algorithm. According to Kozlowski, the math behind the algorithm has evolved significantly. "We have somebody who spends a lot of time gathering comments from customers on people and assignments so the algorithm can be constantly tweaked and properly weighted."

During the development of the algorithm, Kozlowski had an idea on how to develop a similar approach to help OBP determine the best way to move people around within the new structure of DBRRs 1–4. "One of our challenges was having people buy into the new and more flexible organization that was created, independent of product structure and indication," he says. "People really worry about their personal situation, such as who they are going to be working for." Kozlowski put a lot of thought into how to move people around. For example, he first had discussions with all the managers, team leaders, or anyone who ran lab programs. He asked them a variety of general questions to get some idea of their expertise, which helped when determining how to divide them into groups. "I also asked them if there was one person they really wouldn't want to work for," he says. The idea was, whenever possible, to try to keep teams together. "That made moving people around much easier, because unless there was an issue, teams would be moved, not individuals." The expertise data collected by Kozlowski was similar to what was being used in the algorithm, and he developed a simple scoring system that helped avoid the particular mismatches of what people claimed they didn't want. "I came up with a number of models and then presented this spreadsheet to the leadership teams so they could visualize how we could reorganize," he explains. Although he admits the spreadsheet models demonstrated there was really no way to strike a perfect balance among the divisions, they proved very helpful in other ways. "It's a little tricky not talking about who wouldn't want to work for whom," he confides. "But I managed to do that by creating a number of models that I thought were balanced. So, when a manager would suggest moving a person to a different division, they could see how their proposal would change the scores and impact the balance. I don't think I ever had to actually say, "I can't do that because so and so doesn't want to work for so and so."

Kozlowski says the reorganization took more than a year, during which time workloads changed, people left, and new staff were hired, prompting multiple revisions to their calculations. "Still, all of that work on how to move people around created a lot of buy-in when the reorg actually happened." Finally, though he realized that during the initial reorganization that one division may have a bit more experience in one area of expertise, he hopes with training and time, all the divisions will eventually even out.



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Few companies go far in this business without a financial firm on their side. But companies most often experience finance houses first as gatekeepers, not supporters. Seasoned, knowledgeable funders do not take on just anyone who comes in the door; they make informed judgments on the feasibility of early development candidates, seeking to wash as much risk as possible out of their intrinsically risky portfolios. Investment banks, which furnish much of the money for funding companies either directly or indirectly through backing funds, rely largely on the judgment of analysts in the financial firms, creating a true gatekeeper system.

But the financiers vary widely in their preferences for companies and candidates at specific stages of development, from early start-ups with high burn rates to mature players with commercial products. They have created a variety of funding options that allow companies to borrow money against various kinds of assets, some based on market projections.

Our financial roundtable panel, assembled by chief editor Rob Wright at the 2015 BIO International Convention, represents a cross section of financial firms and investment banks, including a Big Pharma-related VC, plus a small company on the funding trail. (See "At the Roundtable.") Many of the firms offer or specialize in the relatively new financing option of "royalty financing," in some ways a simpler, cheaper form of loan-based funding, giving the lending firm a share of future royalties as collateral. The panel discusses how and when the various funding options make sense, as well as changing internal and external conditions for the biotech funding environment.

LENDING'S ROLE

Aside from standard funding sources, such as angels, grants, and VC rounds, under some conditions it makes sense for a start-up or small company to borrow some of the capital it needs. So moderator **Dennis Purcell**, founder of Aisling Capital, first asks the panel to look at biotech investment from the lending perspective:

When and why should a company take on debt?

Todd Schwarzinger of Hercules Technology Growth Capital (HTGC) explains that the loan option is in a "complementary asset class" of funding. For a mature or an early-stage biotech company, loan-based funding can help a company expand in its own way between equity fundraising events, such as taking on an additional set of candidates or to funding internal growth initiatives. Because a loan is a nondilutive form of funding, the company gives up no equity to the lender.

Greg Brown says his firm, Healthcare Royalty Partners (HRP), specializes in royalty financing, as its name implies, with a preference for companies with

approved or late-stage products needing capital for further product development. "If you are receiving a royalty stream or about to receive a royalty stream, lending can give you a higher NPV [net present value] use of that capital." Although the stock market tends to undervalue royalties, "because stockholders have difficulty calculating them, and because they don't believe management will do anything except spend the money," royalty-based lending adds value in Brown's experience, sometimes boosting the stock price after the loan. Thus, royalty financing can both leverage a company's assets and actually raise the market cap over its preloan value.

John O'Meara, part of the fixed income trading division at Morgan Stanley, represents the other end of the size spectrum from HTGC and HRP, but he shares similar views and preferences with the boutique firms, along with caveats: "It's less about companies for us and more about the product itself. For products that are already approved, there is a wide variety of options that we've developed over time to monetize royalty assets. For pre-approval, we've seen a lot of growth in that area. The interest is growing, but it's very much product-specific. It needs to be something that's significantly de-risked or has a uniquely compelling upside profile."

Robert Urban says his Big Pharma-founded investment group, J&J Innovation, prefers the very space the first three panelists approached more warily — and its investment model is not equity-driven. "We do everything in the early-stage space, on behalf of Johnson & Johnson. In 2012, when we launched, we allocated a range of technical expertise to our Menlo Park, Boston, London, and Shanghai sites, because we believed there was a significant gap in the market where we weren't confident of seeing enough progress in all three of our sectors — consumer, medtech, and pharmaceuticals.

"We've done more than 200 investments in the last two years, but only about 45 of them involved equity. When we say investment, it means our putting capital to work, putting people to work, putting the kind of relationships in place that help advance projects toward a licensing or acquisition relationship. We invest only in prospects that we and the innovators believe will benefit from having Johnson & Johnson as a commercialization partner."

BIG BANK OR BOUTIQUE

Purcell directs a question to **Brian Silver** of Perella Weinberg Partners regarding investor size:

> With investment banking, how should companies weigh the prospects of talking to a large firm, compared to talking to a boutique?

Silver delivers a veritable primer on the issue. "If you need access to a capital market to do an IPO, you need to go to a big firm. The big firms are and will continue to be the gatekeepers to the capital markets. That's a very important part of their function, intermediating between investors and issuers." Still, he says, companies commonly have more than one firm advising them on any given deal, because no firm knows all the potential investors or buyers, and different firms bring different relationships to the table.

Smaller firms can pay closer attention to individual client companies as their needs change over time, Silver asserts. "At different points in the company's life you can access different parts of the capital structure, and you need to put together the team of advisors that makes sense for the company at the moment. Regulatory pressure on the large investment banks is heavier than it used to be, so there is a big place in the market, especially in the biotech and pharmaceutical sector and healthcare more generally, for the kind of advice a boutique firm can give."

> *"Regulatory pressure on the large investment banks is heavier than it used to be."*
>
> **BRIAN SILVER**

To bring in the perspective of the small company looking for investment, Purcell calls on **Jeffrey Marrazzo** of Spark Therapeutics, a gene-therapy development company with a novel funding model. Spark was initially financed by the Children's Hospital of Philadelphia (CHOP). After a previous decade of "hibernation," Marrazzo says gene therapy needed a champion, and CHOP, like all children's hospitals, was "disproportionately impacted" by genetic diseases in the patients it sees and decided to step into the role. "The concept was, if we could create a runway to work out some of the challenges that had plagued the field, and that an industry partner or investment firm may not have the patience for, we could make it over to the other side of this special challenge with potentially viable products."

First, in 2004, CHOP established its Center for Cellular and Molecular Therapeutics, mainly as part of its effort to expand its leading role as a "clearinghouse" in gene-transfer research for hemophilia and other conditions. In finding new revenue resources for the hospital and its research centers, Marrazzo and CHOP's CFO, Thomas Todorow, decided to make a bold move into the commercial side with what would become Spark, launched in 2013.

CHOP normally invests some percentage of its endowment in "alternative" or higher-risk investments, largely through fund managers, so it proposed the hos-

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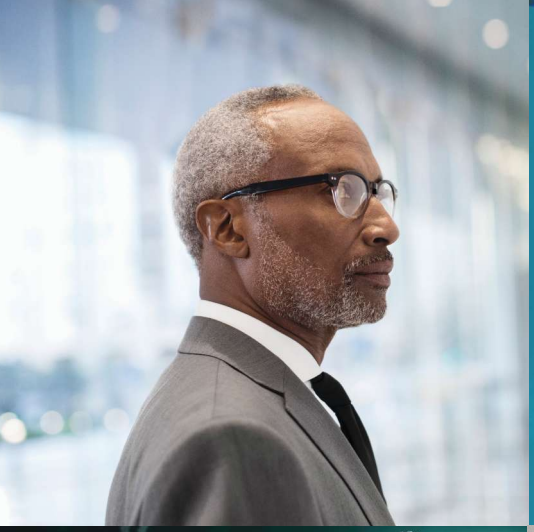

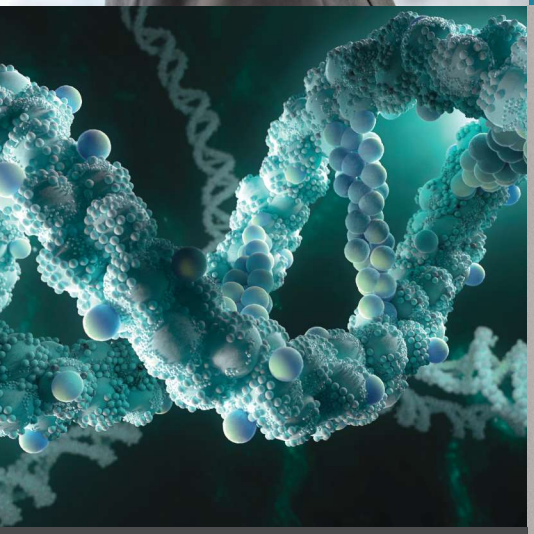

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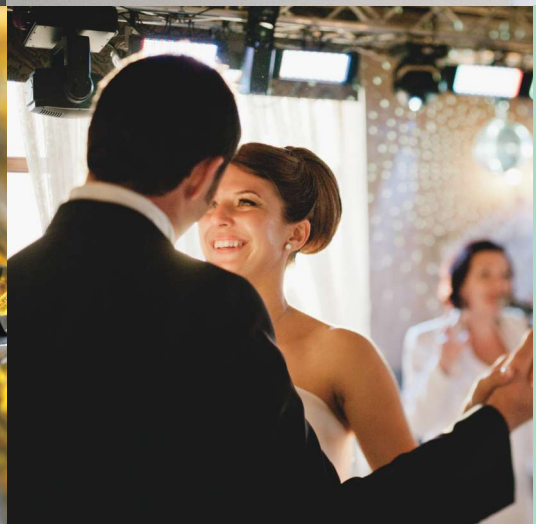

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pital invest directly in the enterprise. Rather than a typical research-funding or technology-transfer deal, giving CHOP a single-digit percentage of royalty or some other return, the deal would be a preferred-stock structure. Once CHOP committed $50 million and put up $10 million for the first round, other investors wanted to join in, so a syndicate led by Sofinnova Ventures funded a second round, with CHOP as the largest contributor.

CLIMATE CHANGE

Turning from funding-model options, Purcell directs the discussion to two larger issues, actually related: Where will new therapies, diagnostics, and devices arise, and under what conditions will someone pay for them?

> Oncology's been hot, but three years from now what will be the one or two hot areas that we are not talking about right now?

Silver tellingly takes a cautious course: "If I knew the answer to that, I would be sitting in one of these investor seats and not in a banker seat. Where the disease burden is heaviest and where progress has not been as strong, such as neurodegenerative conditions like Alzheimer's and Parkinson's, incremental advances can unlock tremendous amounts of value, and we're seeing a lot of early-stage companies there. Orphan diseases have attracted a lot of investment. Will there be a second or third generation of orphan disease companies using small molecules to affect targets now addressable only by replacing proteins or enzymes or similar methods? Of course, another generation of technological advances for gene therapy will replace some of the first generation approaches, which are by now 25 years old in some cases."

The other panelists generally agree with Silver's hot list, so Purcell brings up innovation's gnarly twin — reimbursement. "What will this new outcomes-based payment model in the United States look like? Will it be capitation or pay for success?

"Because the U.S. healthcare system is so complex, all of the possible variations in the new model will probably play out," says Marrazzo. "Reimbursement decisions may drive industry's selection of disease targets to favor those where it is truly possible to transform a patient's life in a measurable way. Ultimately, this is a positive trend for companies that are the most innovative and perhaps provides a disincentive for developing products that only provide incremental benefit to patients."

According to Urban, J&J Innovation is already looking far ahead in its disease-target selection. But the group has narrowed its focus over time, from about 30 disease areas when he arrived about three years ago to about a dozen now. "We made a very explicit, conscientious choice to get much deeper into the underlying biology of all diseases we seek to treat," he says. "We intend to use that information to intervene earlier and earlier, as well as find new biomarkers and other ways of helping us achieve the outcomes those products will be expected to achieve." He elaborates:

"Ancillary technologies have emerged that we might use to capture some of the expected evidence or to become involved in the continuum of care earlier on the device and consumer sides. We have made quite a number of investments in the microbiome space — an out-of-body experience for a big company like Johnson & Johnson. But it's clear to us the microbiome is having a very important, early contributing role in some of the diseases we're targeting."

Morgan Stanley reflects J&J's big-player, long-term focus on selected disease areas, as O'Meara highlights one example: "Away from oncology, our firm has been involved in orphan drugs as a general matter — we did a large monetization for the Cystic Fibrosis Foundation last year. It has been very successful in the investments it made, and it resulted in a large asset for them, to monetize Kalydeco (ivacaftor, FDA-approved in 2012). We've also done a financing recently, for Intarcia, in the diabetes space. Diabetes isn't necessarily a new topic, but they're approaching it in a new way, with a different device and a different approach. Those are some of the things that are more innovative, from our perspective."

> "It is likely that value-based pricing will be where everybody goes, and the utilization of drugs will be far more driven by price."
>
> **GREG BROWN**

Healthcare Royalty Partners, considering its kind of collateral, naturally has a more practical consideration in mind than innovation, at least in the abstract. "Our average investments last around 10 years," says Brown. "What we probably worry about the most is payment, because that is an area where, with an aging population, with a secular diminution in real economic growth rates, payment is becoming paramount."

"It is likely that value-based pricing will be where everybody goes, and the utilization of drugs will be far more driven by price. Probably the single biggest thing that will drive medicine, sadly, is not biology, but economics. Pharmaco-genomics — the ability to stratify diseases based on real genomic markers and to guarantee efficacy within a narrowly constrained population — will be realized. That speaks to value-based pricing as well."

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> *"We've done more than 200 investments in the last two years, but only about 45 of them involved equity."*
>
> **ROBERT URBAN**

Purcell asks:

Are there any diseases less subject to reimbursement risk than others?

"On a pragmatic level, orphan diseases," says Brown. "Let's say you're a health plan with millions of subscribers and you have 12 patients with a lysosomal storage disease, babies who will die if you don't treat them. You don't care how much that costs. There is complete inelasticity of demand, so it is one area not susceptible to pricing. At the other end of the spectrum, I'd say vaccines. The big public health vaccines have a huge impact on herd immunity, as we've seen this past year. There is a lot of inelasticity of demand for vaccines in the developed world. That is generally used to fund vaccine distribution in the developing world. Those are two ends of the spectrum where there is a lot less price sensitivity. Information technology will also play a huge role in enabling the various trends that have come up, whether stratifying patients in some rare diseases or addressing the continuum of care for chronic diseases."

CAPITAL CAPABLE

Assuming a company hits the sweet spot for investors in the ways discussed, it could make one of many common mistakes that would either derail a deal or render it useless. Purcell polls the panel: "Each of you sees a huge number of deals a year. What's the biggest mistake you see, when companies come to see you?"

"Being prepared for capital is the most critical piece," says Schwarzinger. "Coming too early, capital can be challenging to some companies. Being prepared, understanding the opportunity and your long-term funding goals, and picking the right partners are all critical as you're thinking through that process. Just taking the first bit of capital that becomes available to you is not always the best decision."

Silver cites dysfunction in venture-backed boards as "the biggest mistake" in preparing for capital infusion. "Just signing up where you can get the money the quickest or the best valuation at any given moment sometimes is not wise. You really have to think about that dynamic of the old versus the new investors. Can they get along?"

Boards can also confound early-stage financing by pushing too soon to sell the company, he adds. Often, start-up boards contain noninformed angel or family investors who push for a premature sale. "Early-stage companies are not sold; they are bought. When you pass the data event, all of a sudden, people are lining up to buy it. But there is no way to rush that event. If the event hasn't happened, there is no buyer. Once there is an event, then you have a lot of buyers. What really drives the price is the stage and the ripeness of the asset."

Various panel members chime in with a string of responses: Failure to plan for "negative eventualities," such as a failed trial or patent loss, is another common reason a company cannot handle its capital. Optimism is endemic in the industry, simultaneously feeding persistence and inflated projections — a frequent cause for companies' surprise when their capital runs out. And when companies are caught off guard, so are their partners and investors.

"Companies need to have some contingency plan and some idea of how they're going to deal with situations if there's a $50 million funding gap and the last round has a 3X liquidation preference and somebody whose fund is on its last one-year extension owns 40 percent of the stock," someone says.

"We are a strategic investor," says Urban. "The only way that we really make money is by going the distance. Unfortunately, what happens is some company teams underappreciate the complexity of the long haul, especially on a global basis. We're willing to get into these conversations in the earliest moments.

"The other piece that's often underappreciated is the competition. The competition, as we see it, is nothing like what the world looks like today. The competition that we have to imagine is what the world's going to look like 7 to 10 years from now, and it is all about getting your products paid for. You need to have the deepest possible appreciation about what the world might look like. It's a very important component of setting the expectations around the product, and setting the expectation around the team that you need to develop it."

From the company CEO perspective, Marrazzo describes lead-investor CHOP's openness to bringing external experts into Spark's board as independent members, in some cases to replace original members. Consequently, he says the board has become a resource of expertise and advice he can lean on reliably. "Even if you have that optimism gene, it helps if you can turn to some people who balance you at times and ask tough questions about your assumptions based on real-world experience."

INFORMED FORECASTS

Purcell sets off a volley of parting predictions with his final question for the panel:

What would be our biggest surprise, sitting here next year, that nobody's thinking about now?

Silver: "We have been in a climate for a long time, really in the last three or four years, where money was easy to get, where debt, equity, and the markets were very strong. I tell companies they need to protect their assets and think about their downside because the world could change very quickly. This post-crisis liquidity we've enjoyed will not last forever."

Marrazzo: "With people generally getting excited and putting capital into gene therapy, I think we will now see and hear about other potential technologies that can play a role, somehow, together with current ones. There are all sorts of things that could be ancillary or supportive in that context. But there is so much we can do with current gene replacement technology, it will be squarely and continually where our focus is."

Urban: "I've made a long history of never trying to predict the breathtaking moments of science. I don't know what we might be delighted by next year, but I would be willing to bet that we'll see more and more evidence, over the course of the next 12 months, of products that didn't, for whatever reason, turn out to be exciting enough to achieve the hoped-for pricing. We will continue to see more and more evidence that the bar is going up for products to achieve the pricing we hope they will support. That will be the headwind of our world for some time."

O'Meara: "At least until Brian's doomsday scenario, we anticipate an increased interest by investors in pre-FDA assets, simply because that's where the return is and where the yield is, in an environment like this."

Brown: "My folk hero is a little character in Winnie the Pooh called Eeyore. All of you who've read to your children have read about Eeyore, who's a pessimist. I'm with Brian — we've been in a period of incredible liquidity and artificially low interest rates. Nassim Nicholas Taleb has a bunch of black swans sitting in his backyard. Next year we will be talking about one of them. We just don't know which yet. [Taleb authored *The Black Swan: The Impact of the Highly Improbable*.]"

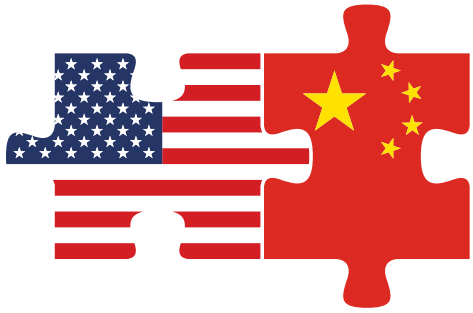
Schwarzinger: "I guess I'm Eeyore's tail — I agree with both these gentlemen. These days of nirvana are not going to last. I don't know how it will end or when it will end, but sooner or later, it will. Typically, when that does happen, the drawback of capital is rapid and very dramatic. The present time is a very nice window for us to be thoughtful about opportunities to apply capital, while it is available. But I wish I knew what will be the catalyst for closing the window."

Purcell adjourns the panel ... until next year? L

U.S. Biotech Meets China Capital: The Next Great Partnership?

LOUIS GARGUILO Executive Editor @Louis_Garguilo

Ambrx Inc., a quintessential American start-up in the emerging biotech cluster of San Diego, founded on revolutionary science spun out of The Scripps Research Institute, was looking for its next round of investment.



An IPO attempt didn't bring in that additional funding, and so the company turned its thoughts to the potential for a merger or acquisition, some eight years after its start in 2003.

What happened next may surprise many. A consortium of brand-name Chinese investors and partners announced a merger agreement with Ambrx, providing sufficient investment to keep the company growing long-term in San Diego, while also opening business opportunities abroad.

ALEX, AMBRX, AND THE ARBITRAGE

Tiecheng "Alex" Qiao was named CEO of Ambrx in June, soon after Shanghai Fosun Pharmaceutical Group, HOPU Investments, China Everbright Limited's healthcare fund ("CEL Healthcare Fund"), and WuXi PharmaTech announced their deal for Ambrx. Qiao is a U.S. citizen who emigrated from China decades ago. In 2006, he left his 10-year career at Kodak in Rochester, NY, put on his entrepreneur's hat, and started founding his own companies, including G3 Technology Innovations and, more recently, NNCrystal in the nanotech space. Meanwhile, business associates and others led him to a renewed interest in China and the growing business opportunities there. "Before I knew it," Qiao says, "I was in China being offered a valuation for my company I couldn't turn down. We made the decision to take the investment from these China venture capitalists."

That personal experience of matching U.S. technology with China capital is a powerful influence in Qiao's life and shapes his understanding of our times. He became more involved in bridging the two countries and became acquainted with Ambrx as a consultant to the consortium that subsequently acquired the company.

"The technology at Ambrx provided a bumpy development ride because it is so revolutionary," says Qiao. That technology is related to a fundamental law of nature: All proteins consist of 20 amino acids. With so few of these building blocks, it's difficult for drug developers to perform modifications from a therapeutic perspective. Upon joining the The Scripps Research Institute in 1999, Peter Schultz, Ambrx cofounder and renowned scientist — and founding director of the Genomics Institute of the Novartis Research Foundation (GNF) — pioneered a method for adding new building blocks to proteins, a so-called "21-Amino Acid Genetic Code." According to Qiao, "The resulting unnatural amino acids allow you to put a chemical handle on a protein molecule and, in theory, put that handle anywhere in the protein." This was a key invention and insight that helped open up the possibilities of therapeutic proteins for companies like Bristol-Myers Squibb, Eli Lilly, Astellas, and Merck, with whom Ambrx has formed multiyear collaborative partnerships.

Ambrx began its applied research with prokaryotic cells, where Schultz had started. (A prokaryote is a single-celled organism that lacks a membrane-bound nucleus, mitochondria, or any other membrane-bound organelles.) Ambrx also extended to the area of mammalian cells, actually assisting in the development of new antibody drug conjugate (ADC) technology. However, it was taking the company longer to find its application for the development of its first drug. "VC funds and private equity in the U.S. have a defined life cycle for their investments in companies," explains Qiao, "and it was now going on 10 years. Ambrx needed to make some financial decisions.

"Think about it," Qiao says. "It's really interest and financial commitment from China that's helping this West Coast biotech take the next step. Now we're moving forward with a strategy to turn the San Diego site into a full-blown innovation center. Our new Chinese partners believe the U.S. ecosystem is the best for this kind of innovation." But the partnership also provides Ambrx a bridge across the Pacific Ocean to leverage all that China has to offer, including its own homegrown science and technology, and to someday – fingers crossed – be a part of commercial markets there. "In my mind, this era of integrating Chinese funding and U.S. technology is a win-win," he says.

"This is an arbitrage opportunity rarely experienced in human history," he continues. "I mean 'arbitrage' in the expanded sense of capitalizing on the advantages – and disadvantages – in these economies and cultures. The key is that both sides benefit equally. There's this insatiable hunger for technology in China, a large amount of available investment capital, and a huge emerging commercial market. Then you have the U.S., the world's leader in entrepreneurism and in producing technology, with a need for more capital to continue to succeed in the largest and most competitive market in the world."

AN ARGONAUT ECONOMY

There are, of course, some people with a less sanguine narrative of current U.S.-China business relations. That description starts with China taking (unfair?) advantage of an open U.S. market with low-wage workers, while its

markets and outside investment opportunities remain relatively regulated. Geopolitics overall can be messy, and global business is not immune to regional realities or global perceptions.

Qiao understands all this and the idea that not all *Life Science Leader* readers will immediately bring a positive viewpoint to an article on Chinese money flowing into U.S. biotech assets.

"My hope is that people recognize China is quickly changing," says Qiao. He believes China wants to move away from being the world's factory center and drive toward an innovation-based economy. He says China recognizes that to become a leading economy you must open up. "Obviously, they must change many regulations … and they are," he insists. "Even though I travel back to China multiple times every year, it's still very difficult for me to keep up with changes taking place, often at a pace that most in the U.S. don't yet appreciate."

Nonetheless, I remind Qiao that the Chinese government still mandates that a drug is invented and manufactured there to be approved for commercial sales. "I'm certain that will change," he says. "For me, as a U.S.-based entrepreneur, I'm less concerned about this because it's coming down to pure economics." And to a large extent, those economics, according to Qiao, are driven by a new breed of international players shaping an open and global economy.

He tells me he subscribes to the thought-provoking portrayal of our current era in AnnaLee Saxenian's book, *The New Argonauts: Regional Advantage in a Global Economy*. Saxenian, known particularly as an astute observer of Silicon Valley, says the scientists, financiers, and entrepreneurs from China (and India, Taiwan, and other countries) have reversed what was once considered a "brain drain" – foreign talent educated in the U.S. but not returning to benefit their homelands. Instead, this talent — and other internationally minded members — have become the adventurers in a new Pacific-Rim "brain circulation." [Editor's note: *The New Argonauts* is worth reading.] Qiao himself embodies these Pacific-traversing argonauts, riding international currents to an enhanced, intertwined knowledge economy, one every bit as vibrant as Saxenian depicted nearly 15 years ago. "Today, it's the Chinese and Indians, particularly," says Qiao, "circling around the Pacific Rim and helping to foster the economies of many countries."

MORE IN THE AGGREGATE

For certain, China has a huge amount of capital that wants to find its way to the U.S. Chinese investment in U.S. businesses, hardly existent some 15 years ago, now totals nearly $50 billion and could reach $200 billion by the end of the decade, according to a study released this May by the National Committee on U.S.-China Relations and the global research firm Rhodium Group. And just as certain the U.S. government takes in more than its share of Chinese money. China held $1.26 trillion in U.S. treasuries in March 2015, according to Treasury Department data. That's the most held by any nation, although Japan and China typically lead in this category from month to month.

Back on the business front, and particular to biotech, Qiao sees this resource disparity as his arbitrage advantage. "Our nation is founded on entrepreneurship; risk-taking defines us," he says. "China has a lot to learn from us, and in this regard, I believe it will take many more years to grasp all the lessons." Qiao believes our biotechnology industry is a perfect teacher and learning ground, and thus we'll see more Chinese investments in our biotechs in the aggregate. "Our industry, in particular, knows how to put a high-tech workforce together and get people to collaborate, from basic conception to product commercialization," he explains.

"My hope is that people recognize China is quickly changing."

ALEX QIAO
CEO, Ambrx Inc.

Always cognizant to even out the equation, Qiao adds that China, in turn, has a lot to offer U.S. companies, well beyond the initial investments. "This current deal allows Ambrx to tap into capital in China, but also additional know-how, lower-cost high-tech labor, and gainful connections in China's fast-growing market, where we would not otherwise have access," he says. "We are still focused on the higher-end markets — the U.S. and Europe — but you can't afford not to think about China anymore. From this perspective, compared to some peers in San Diego, San Francisco, and Boston, we have a competitive edge because of this arbitrage." He concludes: "But you can be sure there will be many others doing deals like this for years to come." L

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How Geographic Expansion Increases Risks

GAIL DUTTON Contributing Editor @GailLDutton

Risk. In the age of social media, biopharma companies have to be more careful than ever about approving or denying compassionate use of investigational drugs. There is no safe "in or out" option. Denying compassionate use can result in a social media crisis, and providing it runs the risk of damage to research and valuation. Either choice opens the company to a crisis of reputation. Thus, effectively managing the risk associated with compassionate use is not only essential, but tricky.

Geographic risks are top of mind for life science executives according to a review of Security and Exchange Commission (SEC) filings by risk consultant BDO. Concern about international threats jumped from 71 percent in 2014 to 88 percent in 2015. "Despite this increase, actual international risks aren't necessarily increasing," says Ryan Starkes, partner and leader of the Life Sciences Practice at BDO USA. Instead, exposure to those risks increases as companies' international activities increase.

"As life sciences companies move and expand operations out of the U.S., there will always be concerns regarding international operations," Starkes says. "This growing concern about international threats, therefore, may indicate that more companies are looking to expand internationally." Supporting that theory, the recent BDO USA, LLP Tax Outlook Survey indicates that 63 percent of its respondents (100 tax directors at companies with market capitalization of at least $1 billion) expect to expand internationally within the next three years.

DOJ TARGETS SMBs

As international footprints expand, companies should pay particular attention to the increasingly stringent enforcement of the Foreign Corrupt Practices Act (FCPA). After targeting Big Pharma for the past five years, the U.S. Department of Justice (DOJ) is turning its attention to small and midsize life sciences companies. As rationale, it cites systematic risks that extend beyond hospitality to include physician recruitment for clinical trials and pay-to-prescribe scenarios.

Smaller firms may be easy targets. Their small staffs often are struggling to return a profit, without compliance officers to focus on preventing FCPA breaches by their employees or agents.

The DOJ's change in focus doesn't let large firms off the hook. They face the same risks and, when acquiring firms, acquire those firms' risk exposure as well as their assets.

VIEWS OF CORRUPTION VARY

"In the past decade, the U.S. has undergone significant changes in how business interactions are conducted and reported," Starkes says. "Foreign countries — with a few exceptions — haven't established as strong a base, which increases the risk of something happening." Those differences contributed to the entanglements of Bio-Rad, Bruker, Eli Lilly, Pfizer, and Schering-Plough.

Part of the challenge, particularly in emerging regions, is that the understanding of what constitutes a bribe or conflict of interest varies among cultures. For example, events or programs that may be acceptable for medical personnel in the U.S. may be considered FCPA infractions when conducted in countries with national health services.

The most frequent misconduct today involves pay-to-prescribe schemes, bribes to gain regulatory approval or to be listed on formularies, charitable contributions, interactions with state-owned enterprises, and work with third-party sales representatives, according to Andrew Ceresney, director of the SEC's division of enforcement, speaking at the CBI Pharmaceutical Compliance Congress in March.

SALES TO FOREIGN GOVERNMENTS

"Life sciences companies are particularly at risk to FCPA charges stemming from sales to foreign government officials (including hospital administrators in government-run health systems)," Starkes says. In regions with government health systems, the FCPA considers medical professionals to be government officials and hospitals to be state-owned enterprises.

Pfizer China, for example, was charged with FCPA violations because it developed a program that awarded points to physicians for prescribing its products. The points could be redeemed for merchandise, including medical books, cell phones, and tea sets. Pfizer, therefore, was charged with providing items of value to government officials in exchange for business.

Charitable contributions also are scrutinized under the same criteria. The Stryker case is an example. In 2013, the SEC charged the medical equipment manufacturer with FCPA violations because (among other infractions) it donated nearly $200,000 to fund a university laboratory in Greece that was favored by a public hospital physician. Stryker paid $13.2 million to settle the case.

In another example, in 2004, Schering-Plough donated $76,000 to a Polish foundation headed by the director of a government agency that funded pharmaceutical purchases and who influenced the pharmaceutical choices made by other medical organizations. Schering-Plough paid $500,000 in penalties.

"The interaction may not be malicious, but intent doesn't release the company from obligations to ensure their employees are following U.S. law," Starkes emphasizes.

Pay-to-prescribe schemes may take the form of charitable contributions, but also service contracts. For example, in 2012 the SEC said Lilly's Russian subsidiary used fraudulent marketing agreements to funnel millions of dollars to Russian officials in exchange for business. In that case, paperwork was accepted at face value with no due diligence regarding purported service providers. Furthermore, the SEC indicated the company had known about the violations in its Russian subsidiary for five years but had ignored the problem. Lilly paid $29 million to settle the charges.

The actions of third-party sales representatives, distributors, and resellers reflect on the company they represent. Therefore, for example, a distributor's representatives placing drugs in a foreign market for an American pharmaceutical company are subject to U.S. laws. The pharmaceutical company is liable for the representatives' actions.

UPCOMING AREAS OF FOCUS

For the future, life sciences companies also need to be aware of the potential for research fraud. The DOJ predicts that falsifying research data to gain marketing advantage will be the next focus of enforcement officials.

There also are concerns that the DOJ or other enforcement agencies will begin mining companies' open payments databases to discover outliers that may tip them off to misconduct. Companies, therefore, should monitor their own data with the same forensics eye that law enforcement auditors would use. That attention extends to monitoring healthcare

professionals to discover unusual financial links to the company.

Life sciences companies also should be aware of the British Bribery Act of 2010. Widely considered the most stringent antibribery law in the world, it stipulates that any entity conducting business "or part of a business" in the U.K. is subject to this law throughout its global operations. This law considers failure to prevent payment of a bribe a violation, thus requiring companies to have strong anticorruption policies in place and known throughout its workforce and among its agents.

STRONG INTERNAL CONTROLS

"The best way for a company to avoid these violations … is to have a robust FCPA compliance program," Ceresney said at CBI's Pharmaceutical Compliance Congress last spring. Often, companies first become aware of FCPA violations when investigating accounting issues or putting internal controls in place.

The DOJ is increasing its focus on financial reporting and in 2014 reported a 40 percent increase in financial enforcement actions compared with 2013. Financial executives and auditors are being scrutinized to ensure financial data is accurate and reliable.

This scrutiny is extending to internal controls. The DOJ has brought charges when it deemed internal controls inadequate in certain areas of operation, such as income tax. The key issues companies face generally are the use of controls that don't match their businesses or that aren't updated as the company and the business environment change.

"The stronger your internal controls, the better chance you have of mitigating risks," Starkes insists. He advises taking a forensics approach using third-party auditors to evaluate payments to determine the reasons for each transaction and to identify patterns and their rationale.

Sarbanes-Oxley (SOX) provides one part of the controls. COSO (the Committee of Sponsoring Organizations of the Treadway Commission) provides the other. The COSO Internal Control – Integrated Framework is used to meet the requirements of Section 404 of SOX.

Available in eight languages, "COSO is the leading guidance for designing, implementing, and monitoring internal controls and assessing their effectiveness. The most recent updates provide a good opportunity for companies to connect the dots among FCPA, SOX, and COSO requirements," Starkes adds.

The 2013 COSO updates expanded reporting beyond finances to internal and nonfinancial reporting. It now includes expectations for governance and reflects changes in business and regulatory complexity, globalization, evolving technologies and, importantly, fraud prevention and detection.

BUILD A CULTURE OF COMPLIANCE

A culture of compliance, aided by an internal framework, minimizes the risk that corruption will go unchecked. "A compliance culture is driven by the core values of top management. It's about constant maintenance and ongoing follow-up — and not overlooking something that appears amiss," Starkes says.

He advises companies to think outside the box and consider the specific controls that are needed given their individual risks and those of their industry. Then, document those controls and ensure the staff understands them in the context of their business. Finally, monitor the controls to ensure the staff responds effectively to business and environmental changes.

Preventing or minimizing the risks of corrupt practices comes down to oversight. "Look at best practices in your industry and in other industries," Starkes advises. "Pay particular attention to common schemes in your industry and geographic area of operations. Evaluate your own operations and brainstorm to identify specific risks and residual exposures. Rank them and map existing controls to them. Think creatively about how those controls could be evaded and ways to prevent circumvention. Then, once a plan is implemented, monitor its success."

Risks are inherent in any geographic area, but as R&D, manufacturing, and outsourcing in general become increasingly global, the potential for violating anticorruption laws grows. Mitigate those risks with strong internal controls and a culture that understands and combats corruption at all levels. L

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Genentech Pushes The Clinical Trial Envelope

ED MISETA Executive Editor @OutsourcedPharm

Having spent more than 11 years at Genentech, Joling Mew has heard a lot of industry discussion about patient-centric trials. Mew is development excellence leader in product development and also works closely with the Strategic Innovation Group. Her responsibilities include leading cross-functional, strategic business initiatives with the goal of driving innovations that will transform the drug development process. In response to the patient-centric buzz, Genentech is testing a new model for clinical trials. And Mew believes it has the potential to transform future studies.

"It is a model that puts the patient at the center of the trial, and its success relies on the patients partnering with us," she says. "Almost everyone, at one time or another, has gone online to search for health-related information. Most everyone also considers their primary care physician to be a trusted partner for managing their health. Both of those factors are relevant to the model we are testing."

Mew notes the current investigator-centric model for trials is slow, especially the time it takes to identify and activate sites. The current model is also often inaccessible to a majority of patients with the target ailment. This is where the Internet and mobile technologies have the potential to transform the way sponsors design and conduct clinical trials.

"Our ultimate goal was to make it easier for patients to learn about and participate in trials," says Mew. "Rather than a sponsor taking the traditional approach of activating trial sites and then having those sites recruit patients, we want to find the patient first and then activate the patient's local care circle."

BECOME MORE PATIENT-CENTRIC

The Internet, along with the growth of biosensors and mobile health devices, created the opportunity to decentralize the process and move from a model that is investigator-centric to one that is patient-centric. Still, for a trial to be successful, Genentech knew it would have to effectively engage with, and mobilize, a patient's local healthcare ecosystem.

In the new model, the process starts with selecting a central principal investigator (PI). This PI has oversight of the entire clinical trial and performs some of the oversight activities remotely, if needed.

Patients are then recruited directly via digital platforms, through their physicians and through patient networks, regardless of their geographical location. Once patients have been identified and express an interest in participating in the trial, they engage their physician, and their local healthcare system is activated. According to Mew, this streamlined process facilitates a patient's participation in the trial since their doctors and other local providers, such as labs or imaging centers, perform many of the assessments and procedures.

Throughout the process, the PI still maintains overall accountability for the trial and treatment decisions according to Good Clinical Practice (GCP). This includes obtaining informed consent and assessing inclusion and exclusion criteria. "The patient's physician is already performing personal care functions, such as physical exams, that we often have to perform in our studies," states Mew.

Mew references the PIVOT (Patient-centric Innovative Vision hOme Testing)

study, one of three pilots that Genentech is currently running to experiment with the ideas of this new model in a lower-risk environment. The PIVOT study is targeting patients currently being treated for DME (diabetic macular edema) or wet-AMD (age-related macular degeneration), two ophthalmology indications. The study involves asking patients to use two mobile phone apps, one that was specifically designed for the study.

In the PIVOT study, there are two arms, which Mew refers to as the traditional arm and the decentralized arm. The decentralized arm is where new patient-centric ideas are being tested, while the traditional arm, run by an investigator, provides the control.

With the decentralized arm, all recruitment is performed online via digital media such as Facebook, Twitter, or LinkedIn. Once a patient learns about the study, they go to the study website, where they complete the screening and consenting processes. Patients who successfully qualify are sent an email informing them of next steps, such as how to download the apps required for the study.

In the control arm, the investigator, who is an ophthalmologist, recruits from his existing patients based on eligibility, and the site staff guides the patients through the consenting process.

In both arms, patients see their ophthalmologist for standard care. During these visits, ophthalmologists are asked to provide Genentech with visual acuity data via the study-specific mobile app. Patients are also asked to test their vision at home twice a week and submit data using an FDA-approved mobile app for vision monitoring.

ANTICIPATE TRIAL CHALLENGES

This new model will not come without challenges. For example, Mew knows that with consent and other processes being performed online, patients have minimal personal support if questions arise. To overcome that issue, in the PIVOT study patients are provided with phone and email support. But that led to another concern: Would patients actually take the time to call or email a contact? And, if they eventually got their question answered, would they go back to the online form and complete it?

Although those questions have yet to be answered, Mew notes those concerns did make the team more aware of the type of information they were distributing. It also made her realize the importance of properly presenting and communicating information to trial participants.

"By cutting down on the number of potential questions, we felt we could prevent patients from having to take time away from completing activities online," she says. "We kept asking ourselves if we were communicating the information in clear and simple-to-understand language, and if we were including all the relevant information that would help patients decide if the trial was right for them."

Another challenge was whether a physician would be willing to support patients in this decentralized model by providing standard of care assessments and performing data entry activities otherwise done at an investigational site. In the PIVOT study, the team wanted to collect visual acuity data from the patient's ophthalmologist, who would normally be gathering the information anyway, by requiring the physicians to enter the data into the study-specific mobile app. To gauge the level of interest in doing this, Genentech performed a survey of ophthalmologists.

Ophthalmologists were presented with the scenario and asked if they would be willing to supply data in support of their patients. The results were encouraging, with the vast majority surveyed saying they would provide the data.

THE LOGISTICS OF REIMBURSEMENT

Mew's team wanted to simplify the entire process for both patients and physicians. So a method had to be devised that would compensate the doctors for their time and effort – a standard practice for all clinical trials – while keeping the workflow simple.

Mew looked at two main options. The first involved compensating the patient to cover those extra costs, and letting them reimburse the ophthalmologist. That would place accountability on the patient and eliminate the need for a contract. However, that could also create an awkward conversation that many patients might not want to have with their doctor.

The second option involved directly reimbursing the ophthalmologist. It would eliminate the patient in the reimbursement process but would also make the study a bit more complicated. Genentech flirted with the first option, but ultimately opted to go with the second. It would keep patients out of the payment loop and allow Genentech to have greater oversight of the entire process. The team then decided the contract with the physician would also be made available online.

"Some readers might question whether we are trying to do too much with the technology in this pilot, but we really wanted to push the envelope," states Mew. "In testing the decentralized clinical trial model, we wanted to understand how willing patients would be to drive the process and conversation with their physicians. By putting everything into a mobile app, we wanted the patients to be able to walk into their physician's office with their cell phone in hand and say, 'This is what I want you to help me with. I need you to input the data here, and I need you to sign this contract.' Everything they need would be right on their smartphone."

Since physicians would first be notified of the trial via their patients, Mew also wanted a convenient way for patients to initiate the conversation. She opted to provide a patient packet that contained, among other things, information about the study and a letter the patient could hand to their ophthalmologists. The letter describes what their role would be in the study and what they were being asked to do. "If that physician is a trusted partner, this should be an easy conversation for the patient to have," says Mew.

WILL PATIENTS PERFORM HOME MONITORING?

A critical component of the trial involved patients performing monitoring at home. For the Genentech team, the question was whether patients would be compliant with checking their vision twice a week using an app that has been cleared for use by the FDA.

For Mew, this concern really revolved around compliance. It was vital that patients complied with the self-testing requirement, since it was a primary end-point for the study. If the tests could be performed at home, they could reduce patient burden and hopefully increase retention.

"Our ultimate goal was to make it easier for patients to learn about and participate in trials."

JOLING MEW
Development Excellence Leader in Product Development, Genentech

"Patients using mobile technologies at home greatly reduce many of the logistical challenges which exist in trials," adds Mew. "That is one of the factors that fueled our desire to undertake this effort. Patients may still have to travel, but maybe not as far or as often, and they are still a central part of the trial. This is something we seemed to keep hearing about from patients."

This new clinical trial model has the potential to not only reach more patients and digitize much of the process, but ultimately be a more cost-effective solution to the standard clinical trial practice. "This study will not be easy, and it is certainly not a slam dunk," Mew states. "At this time we do not know if it will work, or if it will be the best model to use in conducting this type of study. But one of our reasons for doing this is to try to figure that out. In about a year, I hope to be telling you what we learned and whether or not it was a success."

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The Challenge Of Moving From Transactional To Strategic Partnerships

ED MISETA Executive Editor @OutsourcedPharm

Suzanne Besaw's job as strategic alliance manager in Strategic R&D Services Outsourcing for Bayer HealthCare has undergone a huge transition. Eight years ago, she had Bayer's U.S. clinical outsourcing department reporting to her, and there were numerous service providers she needed to manage.

Today, that same department is working with a much smaller number of global strategic providers. While some of the challenges remain the same, others have changed quite dramatically.

When Bayer decided to move from a transactional partnering model to a strategic one, it was a new and novel approach for everyone in the company. Now, after a few years working with this model, Besaw notes personnel are past the shiny-new-penny stage of the strategy. "The initial excitement and adjustment regarding the change has faded," she says. "The company has adjusted well to this change and has demonstrated a commitment to its selected CRO partners that perhaps has not been seen before."

Besaw concedes the change from working with many vendors to a few strategic partners has made her life less hectic. "The number of relationships is certainly easier to manage," she says. "When working with two or three dedicated suppliers, you have the opportunity to set up closer relationships with them. You get to know your counterparts, and they get to know what you want and expect out of them. Those expectations become clearer over time. The main benefit is you are not always beginning a new relationship and having to understand a new supplier every time you start a study."

Of course, when working with a small number of CRO partners, if something does go wrong, it is easy for some to question whether the company should end a relationship and find a new partner. Besaw notes there is also a tendency for employees to question whether the company selected the right partners, and there is always pressure to reevaluate those relationships and consider new ones.

EXPECT COMPETITION FOR CRO RESOURCES

There are certainly circumstances under which a company might want to reevaluate its strategic relationships. Besaw notes she was once in a strategic relationship with a large CRO. At one point in the relationship, she began to have issues with the company, and the timing coincided with the CRO signing a contract with another top 10 pharma company. As soon as that contract was inked, the attention she received from that partner took a precipitous hit. It suddenly seemed like the needs of her company were no longer a priority.

"It was definitely the result of the new contract," she says. "That could not have been clearer based on the time frame. People I used to communicate with regularly were suddenly unavailable to take my calls. Everyone was too busy to do things, and resources seemed very constrained. In the end, we had to end our relationship with them."

If a profitable opportunity comes along, you can't expect your CRO to ignore it. And to the CRO's credit, no business with Bayer was ever guaranteed. About half of the company's trials are conducted in-house. But even when jobs are outsourced, CRO partners are not guaranteed a set volume and must

"When working with two or three dedicated suppliers, you have the opportunity to set up closer relationships with them."

SUZANNE BESAW
Strategic Alliance Manager in Strategic R&D Services Outsourcing, Bayer HealthCare

competitively bid on most trial opportunities. In this instance, the other sponsor company was offering a more steady flow of work. "Even if they only got half of the other sponsor's business, that still would have been more business than they would have gotten from us," she adds. "It was a learning experience for me. Now, when evaluating partners, I look at their size, the amount of interest they have in our business, and how much work they have on their plate."

MAKE YOUR GOALS CLEAR

Besaw admits she has learned a lot about relationships in the time she has spent with Bayer. One thing she has learned is that when working for a large company, people will have different perceptions of how the relationship is progressing. There might be folks at a high level who see the value of strategic partnering and like how the relationship is benefitting the company. At the same time, there might be someone at the ground level who is frustrated and doesn't feel the relationship is working at all.

One way to avoid this disconnect is to ensure the main objective of the partnership is clear to everyone on the team. It should be printed in easy-to-understand language and published for everyone to see. This simple action will help create a better understanding of the big picture for those team members who might otherwise be focused on a small part of the relationship that is not going exactly as planned.

"It can be difficult to see the high-level view when you are working on just one of 30 or 40 trials," adds Besaw. "For that reason, communications relating to the big picture need to get out. Making that information available to everyone can be a challenge, but tools such as a SharePoint portal can be a big help. I have found there is a lot of information that can be shared in that manner, including news, trial information, portfolio metrics, team member names and phone numbers, and much more."

VET YOUR PARTNERS

Deciding on the right outsourcing strategy and partners can be a difficult and time-consuming process. To help with the decision, Bayer looked to a consultant widely used in the clinical space. The firm came in and interviewed key stakeholders on the clinical and procurement teams. They specifically asked these individuals what they were looking for and what they thought was important in a partner. Based on the feedback received, Bayer opted to go with a strategic partnering approach, and then selected two partners based on its volume of trials.

To narrow the pool of CROs down to just two, a request for information (RFI) was sent out to 20 of the largest global CROs. The document was extensive and had a focus on the three key themes that were important to Bayer. The company wanted a CRO with expertise in its therapeutic area of focus, that had a global presence, and that understood the company's data management capabilities. Vendors were

given a couple of months to respond to the RFI.

An analysis was then conducted on the forms that were returned to whittle the companies down to five. Each of these firms were brought in for a full day of sit-down meetings to go through the questionnaire in more detail. These were face-to-face meetings among senior managers of both companies, including the heads of clinical, procurement, and data management.

"We wanted to know if they were interested in a partnership, if they were ready to take part in one, and what value they thought they could bring to the table," says Besaw. "To some extent, a lot of these relationships are still built on trust. We wanted to look them in the eye and determine if they were being sincere. From those face-to-face meetings, the five CROs were narrowed down to the final two."

PROPER GOVERNANCE MAKES THE JOB EASIER

After the two CROs were selected, Bayer designated one a strategic partner and the other a key partner. The key partner was essentially a backup to the strategic partner and through the years has evolved into providing niche therapeutic expertise. Besaw then set up an executive committee that would meet three to four times a year. The committee provided governance to the relationships and was comprised of executives from clinical, regulatory, data management, and other critical areas. The committee allowed all of these executives to work directly with their counterparts at the CRO.

An operations committee that met monthly was also put in place. Several streamlined action committees were also developed to oversee things such as contracting, regulatory, and processing. Their hands-on work helped to determine what was most important to the individual groups. Information they developed would feed into the operations committee, which would then feed up to the executive committee.

"This creates a kind of pyramid in the area of governance," says Besaw. "Once that governance was in place, everything ran much smoother. We now have direct access to their executive management. For example, through the executive committee, we can pick up the phone and call whoever is head of their global operation."

Although the committees simplify dispute resolution, Besaw cautions against giving too many individuals the authority to pick up a phone and make that call. Bayer put an escalation process in place to keep these calls in check. Certain triggers must be hit for the calls to happen. Appropriate individuals are notified, often after an ad hoc meeting takes place to evaluate and assess the incident. An ideal escalation plan would only get senior executives involved when the issue has been raised through the various governance committees without resolution or agreement.

PRICING DISPUTES CAN STILL ARISE

Pricing is always a concern in any outsourcing relationship, with disagreements arising over who should pay for what. Strategic partnerships can actually have the effect of making these disputes a bit more difficult to manage. Bayer currently uses a fixed-price contracting model, with CROs being paid based on meeting-agreed deliverables. They are also held accountable for delivery.

Problems will arise when a program that has in-house experience is outsourced, since researchers have a tendency to tell CROs how they would run the study. When a CRO is told to do something different from what was originally planned, a price increase is generally the end result. Hard feelings can naturally arise when a partner is forced to absorb the cost of something that was not in the original agreement.

Besaw notes it is difficult to get someone who has invested years in a study to hand it over to a CRO partner. She now schedules an open discussion forum prior to locking in a pricing contract. At that forum, she will address concerns employees have over any aspect of the conduct of the trial. Once everyone has agreed on the proper approach to the trial, a contract is signed and a price locked in.

WHEN WILL WE BE READY FOR A CHANGE?

Will Bayer ever need to reassess its strategic partners or partnering model? Besaw thinks the decision can depend on several factors. The first is hedging the amount of risk that exists with current partners. If one of your partners is having difficulty managing resources, as evidenced by complaints received regarding the relationship, it might be time to look into a new alliance.

If you notice an increase in the volume of trials being conducted, that is another concern. Besaw cautions sponsors to also be aware of the number of trials your competitors are launching, since CRO partners may be accepting some of that business. Also keep your eye on the financial condition of partners. A struggling company can easily go under or be purchased by a larger CRO, which may impact your trial. Finally, never underestimate the human components of any relationship, especially trust, respect, and honesty.

"My boss will reach out to the most senior VP at a CRO partner if a situation arises," adds Besaw. "If she says something, she knows she is going to be heard and they will get the concern addressed as soon as possible. They are confident we would do the same. If top executives do not have that rapport and trust, the relationships will have no emotional element. When you lose that emotional element, it is easy for relationships to go south, especially when you are not the biggest client they serve." L

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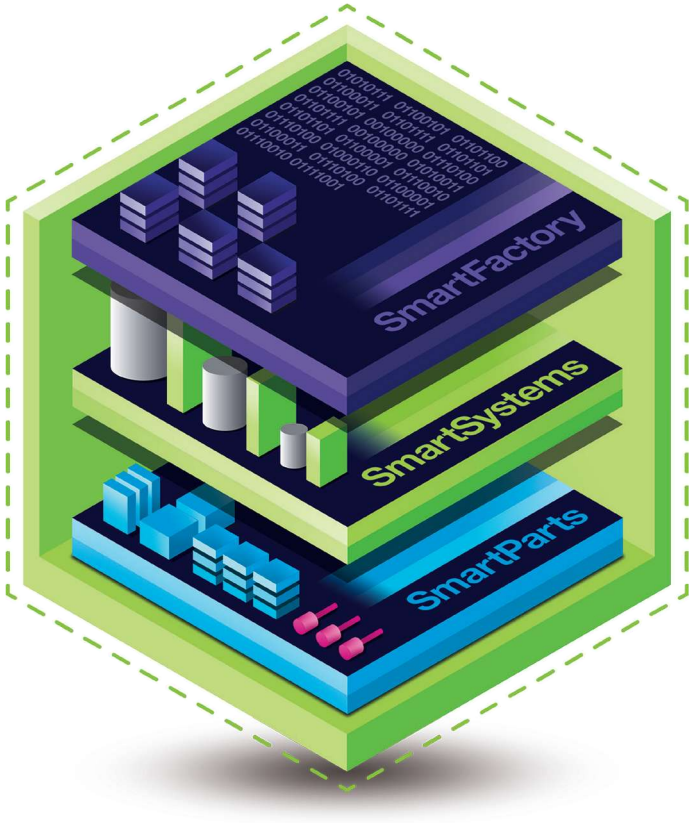

How Advanced Analytics Can Boost Your Commercial Profitability

RIC CAVIERES

"What is our commercial profitability?"

That's a question biopharma executives have long struggled with due to an inability to analyze the true cost of drug commercialization.

The issue of commercial profitability has been further complicated by an evolving healthcare landscape that includes an increased focus on costs and the shift in decision-making power toward payors, an increase in discounts (via rebates, co-pay cards, patient assistant programs), multichannel marketing, and new organized customer models such as integrated delivery networks (IDNs) and accountable care organizations (ACOs).

Fortunately for biopharma, the increasing complexity of commercial spend is paralleled by an increasing availability of data. The companies that can successfully leverage this data via advanced analytics will gain a competitive edge and increase their commercial profitability. Considering a 1 percent increase in commercial profitability equates to nearly $400 million for a top 10 biopharma, companies are jumping on board to incorporate commercial profitability into their business to significantly boost their bottom lines.

WHAT IS COMMERCIAL PROFITABILITY?

Biopharma struggles with assessing true commercial profitability because the industry typically lacks a holistic view of its commercial spend. For instance, various types of commercial spend (including payor rebate, wholesaler discounts, patient co-pays, physician samples, marketing spend, etc.) are only being tracked within the siloed business functions of sales, marketing, and market access.

Market access typically measures performance with the gross-to-net (GTN) metric and only takes into account discounts to payors, wholesalers, pharmacies, and institutions such as long-term care (LTC) and hospitals. This methodology accounts for rebates and chargebacks but misses additional discounts given as patient co-pay discounts, which is typically owned by the brand and patient assistance programs (PAPs). The brand and sales teams typically focus on market-share metrics, total prescriptions (TRx), and new prescriptions (NRx), but these metrics do not account for the discounts or the commercial OPEX spend to drive these sales and market share. True commercial profitability must take into account all commercial discounts and spend:

"On average, 49.5 percent of gross revenue is spent on commercialization, or almost 50 cents on every dollar."

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− DISCOUNTS &
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= COMMERCIAL PROFITABILITY

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- **DISCOUNTS** = rebates, chargebacks, admin and other fees, patient co-pays, and PAPs
- **COMMERCIAL OPEX SPEND** = sales force spend, including samples, marketing, and brand spend, including DTC (direct to consumer) campaigns; all multichannel and speaker programs; and sales, marketing, and market-access people spend.

Failure to look at commercial profitability holistically presents specific challenges to optimizing spend, ultimately resulting in the potential for both overspending and suboptimal sales.

BENCHMARKING, CURRENT COMMERCIAL PROFITABILITY, & FUTURE STATE OPTIMIZATION

The key to effectively leveraging your disparate data sources lies in defining and standardizing spend and allocating it at the same level of gross sales so that commercial profitability can be measured at the granularity of geographic zip code, customer, brand, and segment (Figure 1).

Once commercial profitability has been measured and benchmarked, the next step is to determine how to optimize both spend and commercial profitability. Innovative commercial optimization models have been developed to help biopharma companies gain insight into opportunities for reducing wasteful spend and investing in revenue-generating efforts. These analytics models use algorithms that correlate and weigh the input levers (various types of spend allocated at appropriate levels) and the desired outputs (commercial profitability, sales revenue, market share, patient access) while accounting for the market factors (e.g., demographics, payor positioning, and brand saturation) impacting the correlation. In effect, this approach to determine optimal, future commercial profitability is driven by Big Data and focused on advanced analytics.

These insights are of tremendous value to brand teams as they budget future spend across multiple marketing channels and customer types, as well as for the field sales force budgeting and deployment. These same insights also drive the decisions regarding brand targeting to customers and market-access optimization through customer discounts. Taken together, these insights introduce a holistic commercial spend allocation optimally aligned to drive a predetermined commercial profitability target.

To more clearly illustrate the real-life value driven by these analytics, consider that the top 20 biopharmas spend, on average, 28 percent of their gross revenue on discounts and 30 percent of net revenue on SG&A (selling, general, and administrative) costs. On average, 49.5 percent of gross revenue is spent on commercialization, or almost 50 cents on every dollar. Optimizing this by just one commercial profitability point will drive $400 million per annum. A few examples of where that $400 million would come from:

MULTICHANNEL

- Based on average pharma sales force size and spend per rep, EY estimates that $60 million in profitability can be gained by allocating promotional spend to more appropriate customer channels; we have seen up to 10 percent savings resulting from optimization of multichannel investment dollars.

CAMPAIGN EFFICACY

- The top 10 biopharma companies spend close to $98 billion on overall sales force promotion and advertising, with $3 billion spent on direct marketing to consumers and $24 billion on direct marketing to healthcare professionals. Given the increasing challenge for sales reps to reach physicians (a Medical Marketing and Media industry survey indicates 23 percent of physicians refuse to see reps), EY estimates the industry could experience savings of $1.5 billion by reducing face-to-face detailing spend by just 10 percent. With greater insight into cost-savings opportunities, biopharma can greatly increase its commercial profitability not only through cutting unproductive costs, but reallocating these costs into campaigns that are anticipated to increase sales.

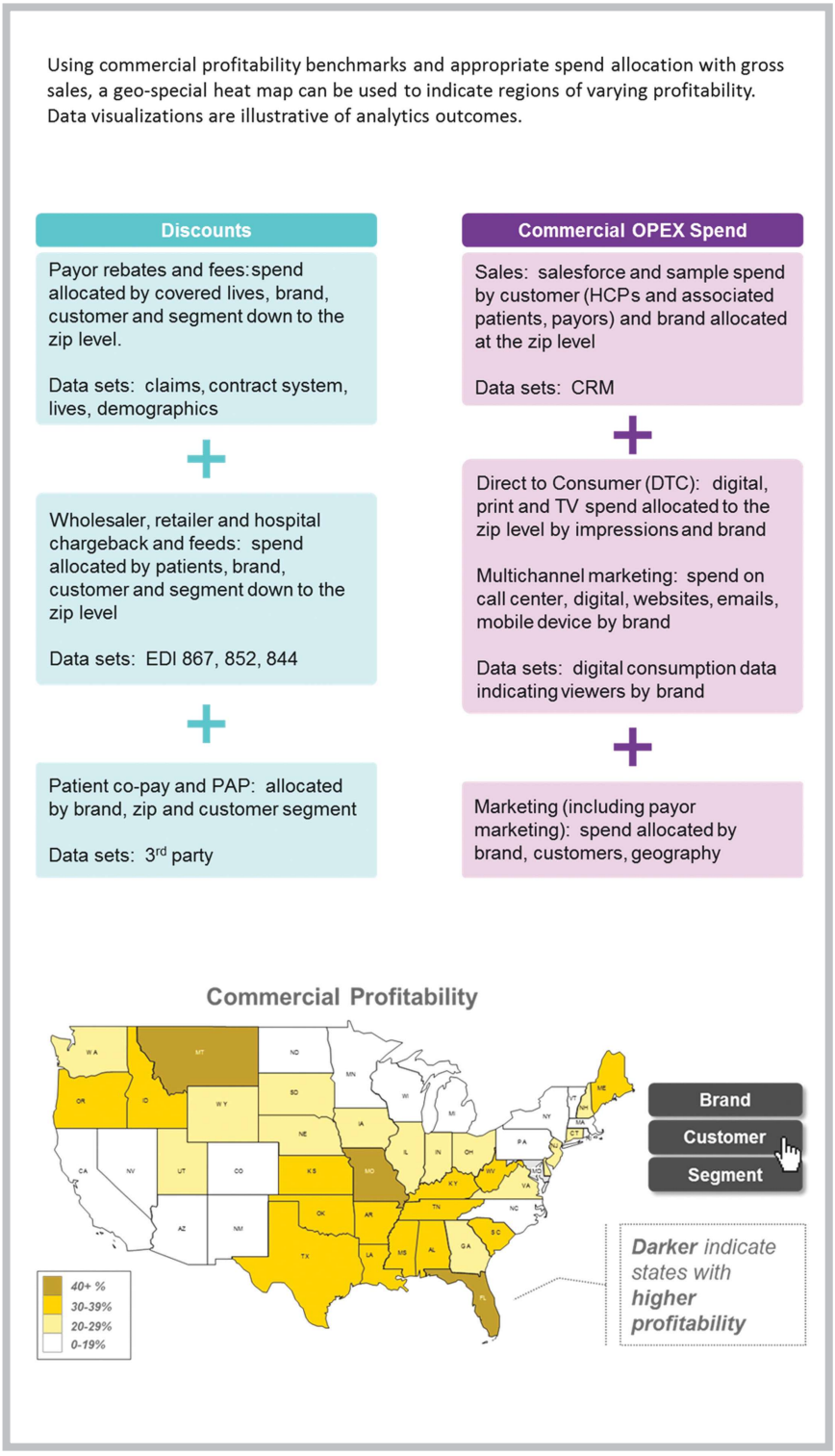
PATIENT CO-PAY

- One pharma company discovered that by optimizing patient out-of-pocket spend (through co-pay programs), it could increase gross sales over $10 million by focusing on less than a dozen geographic regions that were underperforming.

UNITING THE CFO AND COMMERCIAL OFFICES

With the insights generated from predictive models, commercial and finance teams can collaborate more effectively and

FIGURE 1



generate granular budgets to drive targeted commercial spend. These insights also tell commercial leaders how to allocate their budgets into geographies as well as help those leaders create action plans for their sales forces. This includes field sales force alignment and investment, marketing and multichannel channel allocation, DTC campaigning, and discounting and contracting strategies. Brand leads will see where they have opportunities to optimize and can leverage these insights to support requests for additional budget as needed. On the finance side, there is increased visibility into where budgets are being spent, with more detail around anticipated ROI of various commercial spend channels. With these insights, the finance office will have better data to support its spending decisions across the organization and be able to more accurately forecast the anticipated resulting revenue and profitability. The resulting process unites the CFO office and the commercial business through the enablement of the common metric of commercial profitability and understanding of business levers that drive such profitability. Together they can work toward the goal of driving the next 1 percent of commercial profitability.

Ric Cavieres is a principal in the Life Science Advisory Practice at EY and leads EY's Americas Life Sciences Commercial Practice as well as EY's CASE (Commercial Analytics Suite) globally. Ric's Twitter handle is @RicCaviresEY, and you can contact him at ric.cavieres@ey.com.

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The Challenges Surrounding Immunology

QIAN SHI, PH.D.

Qian Shi, Ph.D., is head of cancer pharmacology at Crown Bioscience, a drug discovery and development service company.

Immunotherapy is a growing trend within the oncology industry, as the traditional processes, methods, and equipment used in the fight against cancer are evolving and adapting constantly in order to try to find the most effective cure. Traditional treatments like chemotherapy and radiation remain effective methods of fighting the disease; however, recent research has started to shift away from aggressive indiscriminate treatments toward more targeted therapies.

WHY IS IMMUNOTHERAPY IMPORTANT FOR TREATING CANCER?

It is well known that cancer has immune components; however, recent advances in research have shown that certain mechanisms of immune suppression of cancer can be reversed, resulting in the reactivation of the immune system to recognize the tumor cells and kill them. Traditional therapies are limited, as resistance can quickly arise; however, attacking a tumor with an activated immune system results in a durable response. Patients can survive longer and may even be considered cured, fueling demand for new therapies in this area.

CURRENT TRENDS IN IMMUNOTHERAPEUTIC RESEARCH

There has been a recent upsurge in immunology due to the clinical success of checkpoint antibodies, such as anti-PD1/PDL-1, which restore immune function in the tumor microenvironment. Some of that success includes certain patients affected by difficult-to-treat cancers, such as melanoma or lung cancer, experiencing a long-lasting response, which is a striking outcome never observed before, thus driving the recent research expansion in this area.

There are three main trends in immunotherapeutic research, the first being diversification. Immunotherapy has become more diversified, leading to increased competition. Different mechanisms and therapeutics approaches are being explored, such as immune checkpoint inhibitors (such as anti-PD1/PDL-1 antibodies), adoptive cell transfer of T cells with chimeric antigen receptors (CAR-T), and tumor-infiltrating lymphocyte vaccines.

The second trend is combining immunotherapy with traditional treatments, such as radiation, chemotherapy, and targeted therapies. The aim is to widen the relatively small responder population of a certain cancer type and to expand the application of combined treatment to other cancer types that may not have been previously considered immunogenic. By combining traditional therapy with immunotherapy, researchers believe cancer cells will become more immunogenic and, as such, more easily recognized and attacked by the immune system, leading to better and more durable responses.

Finally, predictive biomarkers of response are increasingly being adopted to identify the patient population that is most likely to benefit from a particular treatment regimen.

THE CHALLENGES OF DEVELOPING IMMUNOTHERAPEUTICS

Developing immunotherapeutics has various challenges, the biggest being identifying the appropriate animal models to evaluate efficacy and predicting toxicity *in vivo*. A lack of experimental models with a functional immune system for preclinical evaluation has significantly hindered immunotherapeutics' development. Mouse syngeneic models, in which murine tumor cell lines are grafted into an immunocompetent murine host, are widely used to evaluate the efficacy of therapeutic molecules. However, this means that a molecule that targets a mouse model has to be used as a surrogate. Therefore, the translatability of the results is also debatable. Researchers have been working on developing humanized mouse models to address this issue, and although there are some promising results, most of the humanized models suffer from low reproducibility and lower efficacy due to the intrinsic complexity of these models. Furthermore, developing biomarkers for immune therapy, whether that is predictive pharmacodynamics or prognostic markers, has proved difficult due to the complex nature of this therapy and underlying mechanisms. With only a specific subset of patients benefiting from an immunotherapy agent, it is important to find those biomarkers for patient stratification, especially considering a patient's immune system is complex and may evolve over time.

Advancements in immunotherapy are causing regulatory agencies to quickly adapt to the new scientific evidence and modify regulations accordingly. A good example is in clinical trials, where patients undergoing immunotherapy may experience an increase in tumor volume at the beginning of the treatment before tumor shrinkage. This is due to infiltration of immune cells into the tumor mass, resulting in an apparent volume increase, which under previous regulations and clinical criteria would have terminated the treatment. Other regulatory issues include the need to educate patients and physicians regarding potential toxicities of immunotherapy, which may depend on the type of treatment used. The treatment can be more aggressive and systemic, causing higher toxicity levels, but also a higher cure rate.

Regardless of these challenges, immunotherapy is a rapidly developing industry with striking results, which could transform cancer research and provide cures for a large number of people diagnosed with cancer.

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Does Demand Forecasting Keep You Awake At Night?

JIM MULLEN

James Mullen is CEO of Patheon N.V., a global CDMO. Before Patheon, Mr. Mullen was CEO and president of Biogen.

Given the uniquely long and winding road pharmaceuticals must take to market, it is difficult for developers to predict the manufacturing capacity they will need when their product finally gets there. Necessity demands that developers begin thinking about production capacity around three years prior to launch, but at that time a company has no real idea if its product will be a success, or how big a success, and therefore how much capacity it will need. Will it need a million units, 10 million, or 50 million? Guess wrong one way, and the company has a white elephant and a massive loss on its investment. Guess wrong the other way, and it misses out on irreplaceable revenues.

To estimate future needs, pharma companies develop forecasts, and often quite sophisticated ones, too. But, by definition, forecasts are never 100 percent right. And it's especially difficult to predict sales in markets that are likely to see the introduction of numerous competing products.

One way to solve that problem and relieve that uncertainty might be for a developer to outsource production to a CDMO. But those of us on this side of the fence historically have behaved as though it is our clients' job to tell us how much product they will need. As long as we think that way, the risks of over- and under-capacity remain, threatening both revenues and profits.

Instead of forever seeking more-certain forecasts, I believe we should be talking about how to provide flexible, scalable capacity that can accommodate the uncertainty. With sufficient flexibility, the need to accurately forecast demand for a product that does not yet exist is relaxed.

YES, YOU CAN HAVE IT ALL

There are several ways to provide flexible manufacturing capacity cost-effectively. Developers, especially larger ones, can do it themselves, and I believe CDMOs also are well positioned to do the job.

The first requirement is scale. If you have many plants and lines, it is pretty simple to accommodate unexpected demand by validating more product lines in more locations than you expect you will need. That capacity can be used for another product if that demand does not materialize. The manufacturer can distribute and mitigate the risk of over- or under-capacity for any one product.

It is also relatively easy to provide flexible capacity for biologic drug substances. For a new biologic, a typical forecast range might be 2 million to 10 million units a year. If you build capacity for 10 million units and the demand turns out to be 2 million, you will pay far more overhead than you need. If the launch is a runaway success and demand rises to 15 million units, then you forgo 5 million units a year in sales at say, 90 percent gross margin. However, with multiple single-use 2,000L reactors, you can flex capacity as you need it. Single-use technology does not require revalidation of additional reactors because the process is exactly the same in each, and the ramp-up time for an additional process is short. So capacity can be easily flexed within a facility or across more than one location.

Flexible capacity is not so easy to achieve for small molecules, as each has its technical challenges and requires certain assets in every location. One way around this (other than to invest in assets that may not be needed) is to recruit third-party manufacturers. There are many of these that make just a few products for a few clients. A large manufacturer that already has strong quality and technology transfer capabilities can assimilate such companies into its network and impose its standards and ensure scalable capacity, quality, and delivery.

The pharmaceutical industry is in a period of rapid change. Scientific and technological breakthroughs, changing regulatory requirements, payer pressure, patient demands, and rising costs are all leading to more challenges for developers. To focus on these challenges, it is important we eliminate whatever other risks we can. I think that demand risk is eminently manageable at a reasonable cost. And I think we'll all fare better if we think of it as a risk we can manage by flexing capacity, rather than one we can eliminate with a better crystal ball . L

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Barbara Tardiff,
Vice President, Global Head Clinical Innovation and Informatics,
Pfizer, USA

Partnerships in Clinical Trials Question Time

Dr Guy Yeoman,
Vice President Patient Centricity,
AstraZeneca, UK

Paulo Moreira,
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Public Speaking:

The Critical Leadership Skill

LENNY LASKOWSKI

Most leaders today are often evaluated by their abilities to speak effectively. If you listen to effective leaders, one of the skills they possess is their ability to speak in public. Becoming a better speaker is a learned skill and an art. Many of today's leaders were not good public speakers earlier in their careers.

Unlike reading and writing, public speaking is not one of those basic skills we are taught during our school years. To those with no public-speaking experience, often they feel their only option is to write out their entire speech word-for-word and memorize it. Of course, that's not an easy task, and it's time-consuming. Furthermore, most of us don't write like we speak. So when we try to speak the words we wrote, it feels — and sounds — awkward.

As a result, many of us fail at our first public-speaking assignment, which leaves us with a lot of negative feelings about public speaking. As we get older we avoid public speaking altogether due to this first negative experience. The good news is, we can all become better speakers with the right tools and guidance.

Here are a few short tips on becoming a better speaker (and leader):

1 NEVER MEMORIZE YOUR SPEECH OR PRESENTATION

Instead of memorizing your talk, think about the key points or concepts you want to discuss and just talk about them conversationally.

2 USE CONVERSATIONAL LANGUAGE

Learn to just have a conversation with your audience. When we approach speaking as a performance, we are worrying more about what the audience is thinking and not focusing on just having a conversation.

Lenny Laskowski is a leading authority on public speaking and a national best-selling author, keynote speaker, and seminar leader.

3 PRACTICE AND REHEARSE

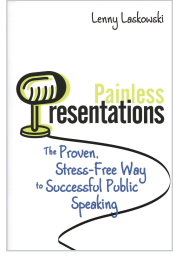
Most people do not rehearse or practice their presentation. Practice your presentation out loud. Record your presentation and play it back and take notes. Listen to what you said and how you said it, make changes and adjustments, and then repractice and rerecord the presentation until you feel comfortable with what you are saying and how you are saying it.

4 FOCUS ON YOUR MESSAGE

Do not focus on the audience. Focus on your message and how to effectively deliver that message. Remember, the audience wants you to succeed. If you find yourself thinking about yourself, how you sound, how you look, etc., you are taking away the focus on your message and your nervousness increases.

5 TAKE A PUBLIC SPEAKING CLASS

The quickest way to improve your public speaking is to take a public speaking class. Read about how to do presentations and how to improve your public speaking skills. Work with a professional who can give you the proper guidance and help to improve and practice what you are taught. Becoming a confident public speaker is achieved only by focused effort and a lot a practice. The good news is your payoff will come quickly, you'll have fun along the way, and the confidence you develop will improve virtually all areas of your life. L



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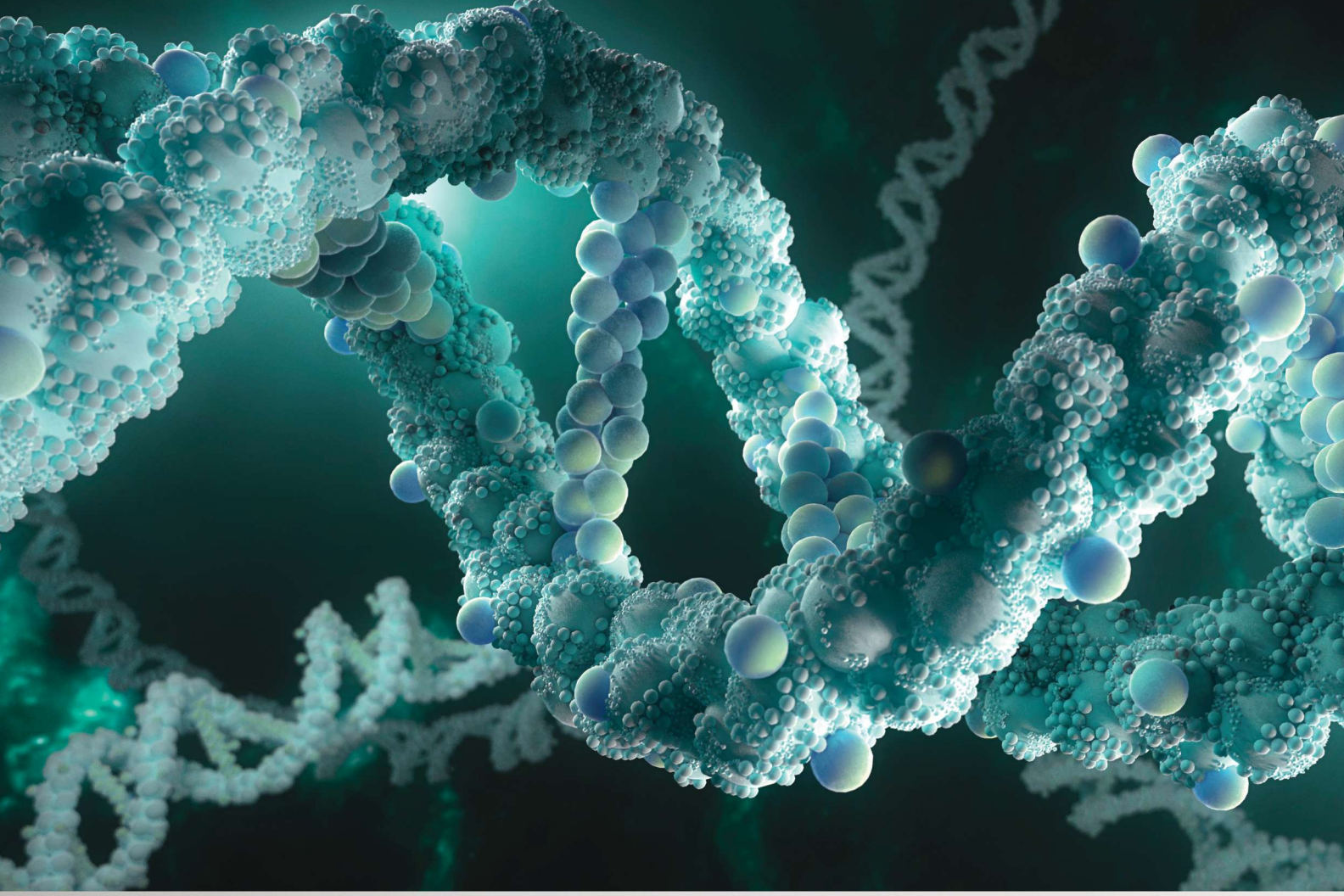

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