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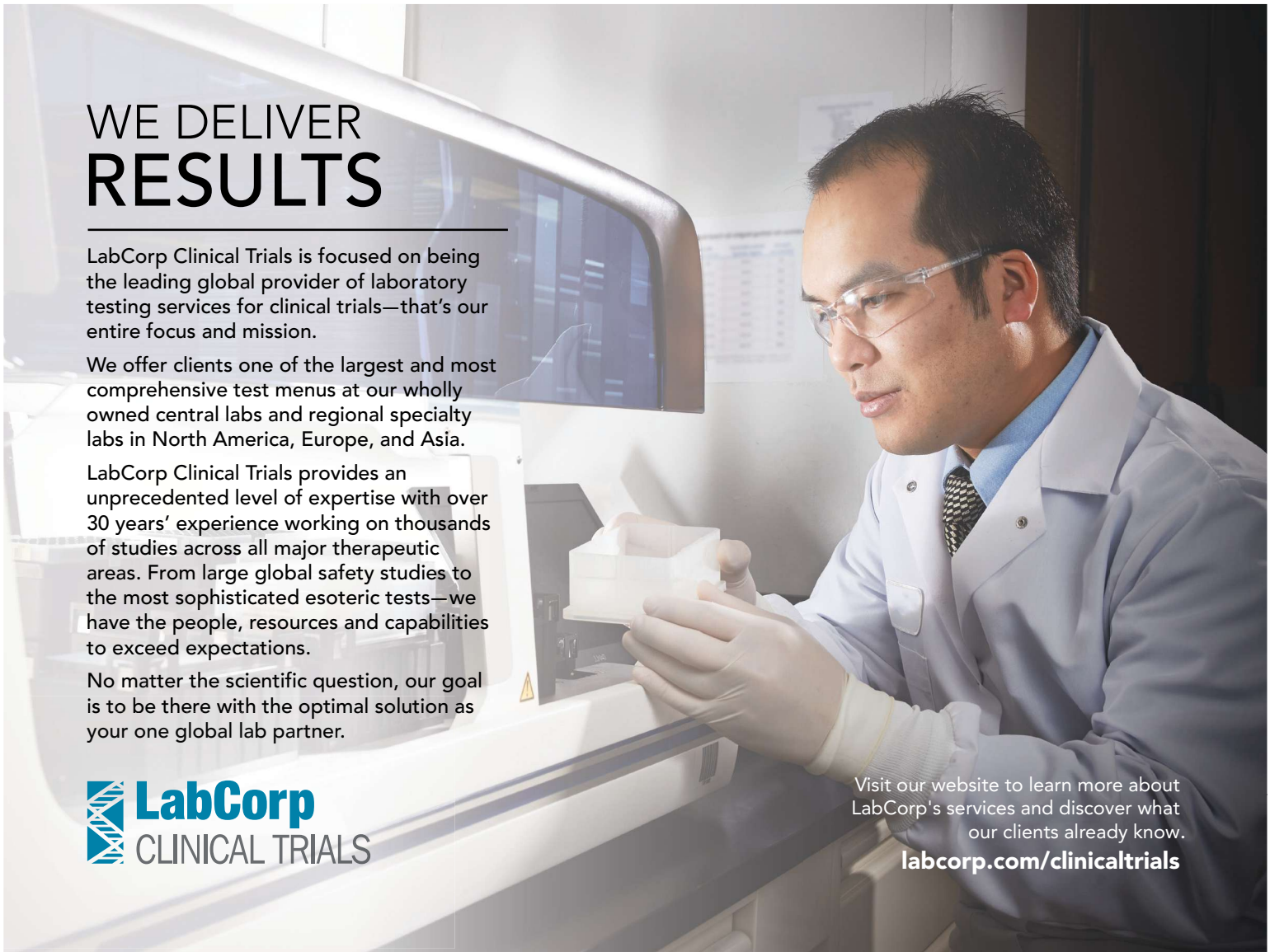

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Creating Start-Up Style Innovation at GSK

Dr. Patrick Vallance, president of pharmaceuticals R&D, leads reforms through all stages of drug development. **p. 24**

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Life Science Leader

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Online Exclusive

Chief Editor Rob Wright recently was invited to attend a private dinner hosted by the National Journal that included top executives from companies such as AstraZeneca, Lilly, and BIO. The focus of the dinner discussion was personalized medicine.

Read Rob's insights from the dinner at his blog at www.lifescienceleader.com/blog/robs-blog.

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Want To Forever Alter The Course Of Your Business?

ROB WRIGHT Chief Editor

Have you ever had an experience that forever changed the course of your existence? I know I have. When you think about things such as how you met your significant other or why you are working where you are, you realize the significant role human decision making plays in determining or altering your course. Advocates of predestination contend that free will does not exist based on the assertion that you did not choose to be born. I do not subscribe to this notion that either the destiny of your life or the success/failure of your organization is preordained.

Chaos theory not only teaches us to expect the unexpected, but more importantly, that small changes made early can often drastically alter outcomes. This principle is popularly referred to as the butterfly effect and attributes the power to cause a hurricane off the coast of Mexico to a butterfly flapping its wings in India. In the business world, I contend the existence of *Course Changers* — human butterflies who can and do dramatically impact outcomes and alter courses well beyond their immediate environments. To find them, however, you probably need to look outside of your industry. For example, Candy Lightner founded Mothers Against Drunk Driving (MADD) after her 13-year old daughter was struck and killed by a hit-and-run drunk driver in 1980. Since then, Candy has been influential in everything related to eliminating drunk driving, from the passage of laws imposing fines for drunk drivers to the enactment of the National Minimum Drinking Age Act of 1984.

While you might be thinking Steve Jobs and Bill Gates are Course Changers, citing their outsider roles and *significant* impact on the music industry (i.e., Apple/iTunes) and global health (i.e., the Bill and Melinda Gates Foundation), they had significant financial and social status advantages to get things done. Lightner had no law enforcement, legal, or political experience, and yet with limited financial resources was able to change the status quo.

True Course Changers aren't just outsiders too naïve to know the rules of your industry, but highly motivated people often moved to action by personal tragedy. There's no doubt that, with the challenges facing our industry today, we could use a few more Course Changers. They are out there, as I discovered when I interviewed the leadership team of PatientsLikeMe for my feature story this month on page 30. Their story is very similar to Lightner's. The co-founding brothers Jamie and Ben Heywood were inspired by tragedy (i.e., their brother Stephen's diagnosis and decline from ALS). They are outsiders, mechanical engineers who aren't buying into the notion "It is what it is" when it comes to how healthcare is delivered, drugs are developed, and clinical trials are executed. The PatientsLikeMe team has built a data-sharing platform they believe will change the way patients manage their own conditions and transform and align the relationship between patients, physicians, and biopharma. If you want to change the direction of your business and our industry, perhaps it is time you listen to the ideas and perspectives of a few Course Changers, for they do not believe as you, nor do their beliefs require you to agree with them — and that could be all the difference you need.

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Q What Is The Best Leadership Advice You Ever Received?

A "YOU BEHAVE THE SAME WAY whether you are the center of attention or when no one is looking, so you have character – and character counts." This thought was communicated to me in a letter from a former boss, Robert Capizzi, who was CMO and head of R&D at US Bioscience when I worked there in the early '90s. He spontaneously sent me this note about five years after I left the company. Although not directly intended to be leadership advice, it had a profound impact because it made me realize how important authenticity is in a leader and that character is also reputation. As a result, I continuously assess my behavior for consistency and objectivity, and I look for these traits in my colleagues.

MARY ROSE KELLER
As a former VP of clinical operations, Keller has proven success in planning, management, and delivery of global phase 1 to 4 clinical trials for drug, biologic, and diagnostic products.

A ONE OF THE MOST USEFUL WAS "... to develop a leadership model that reflects my values, my leadership philosophy, and my style and then use that model to become a more effective leader." My first clinical development manager said such an approach would serve me throughout my career. It took a while to develop that model, and while I continue to tweak it, he was correct. My philosophy is servitude, the leader as a servant. My style is situational, adapting my approach to best affect my team and what it is we are trying to accomplish. As my philosophy and style developed, so did my model of leadership. As my boss and mentor predicted, when my leadership is not having the desired impact, I revisit my model, analyze my actions, and if necessary, adjust.

TIM KRUPA
Krupa is president of TSK Clinical Development, a consulting firm providing leadership and solutions in clinical planning, project management, clinical operations, and outsourcing. He began his career with Eli Lilly, and he most recently served as executive director, project management with Quintiles.

A I RECEIVED IT FROM KARL BRACHT, former divisional president at Sartorius. His advice was "Treat every person in an organization as important and respectful as any other, no matter what title or status." I believe this not only applies to the business side of life, but also to the personal. An organization is like a clock, every wheel and every part counts, no matter how small or large. If one part does not function, the clock does not work. It is often forgotten that the most valuable asset in a company are the people, all of them, and especially when they work as a team. They must respect, value, and support each other. Only a happy and content organization will supply the best product and services to its customers, and only such a team will go the extra mile for the customer.

MAIK JORNITZ
Jornitz is COO of G-CON Manufacturing and founder of BioProcess Resources. He has more than 25 years of experience and supports the biopharm industry on a global basis, focusing on validation, optimization, and training in aseptic processing.

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What A Republican Senate May Mean For Health Policy

JOHN McMANUS The McManus Group

Just days before the election, the president's approval ratings are at an all-time low, and Democratic Senate candidates are running *against* the president, with the Democratic candidate in Kentucky refusing to disclose whether she even voted for him, claiming a constitutional right to privacy. If the trajectory holds, the Republicans should take the Senate and control both houses of Congress.

What would this mean for health policy for the last two years of the Obama presidency?

A new Republican Senate majority will likely move early to try to repeal Obamacare. But even in the minority, a unified Democratic conference can block an up or down vote from proceeding. Even if Republicans peel off the necessary Democrats to reach the 60-vote filibuster-proof super-majority, the president will be sure to veto a repeal of his most cherished domestic legislative achievement that now bears his name.

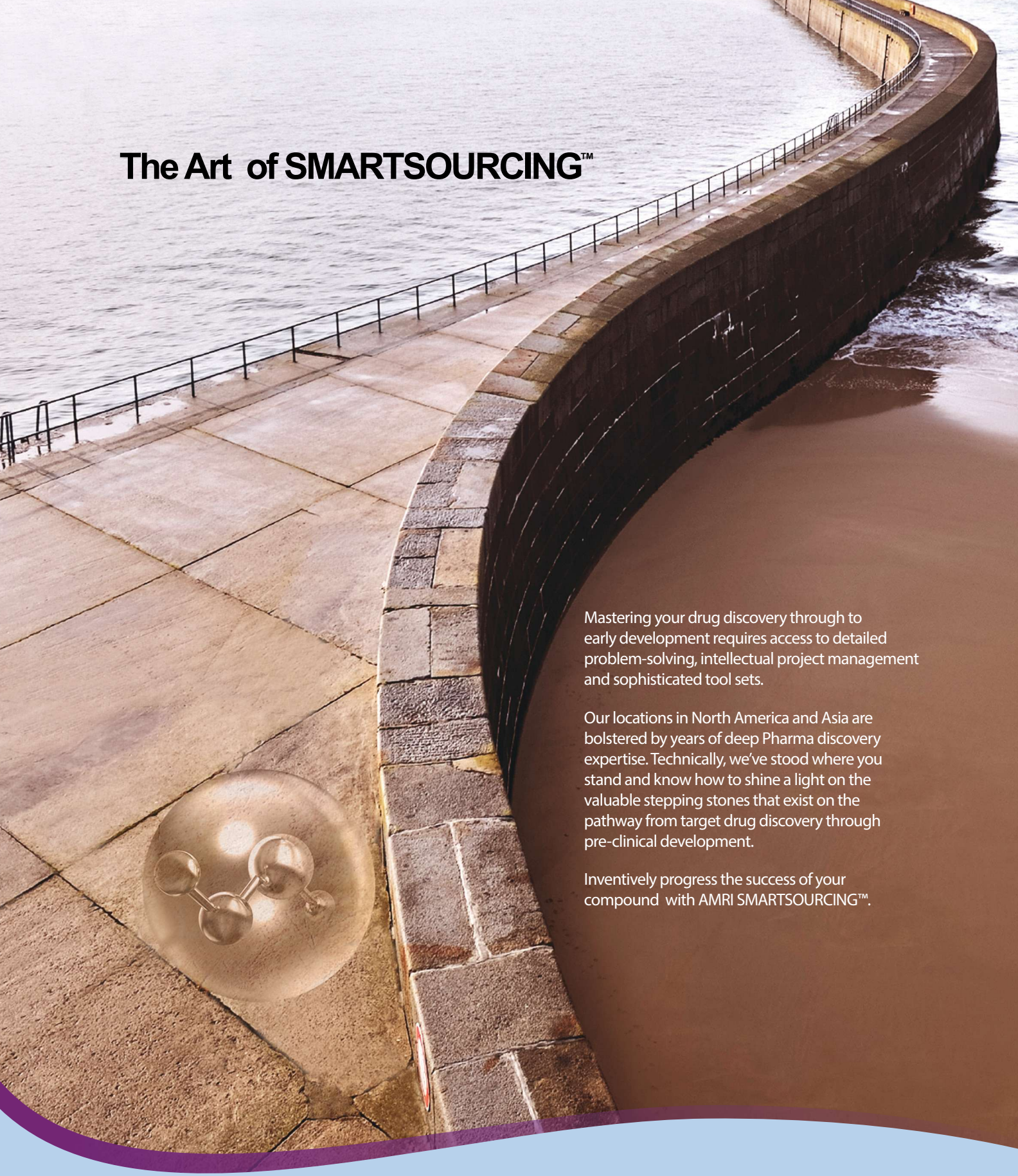
Following this fruitless exercise, Congress could tackle real issues.

The present "SGR [sustainable growth rate] patch" blocking massive, pending Medicare payment cuts for physicians is set to expire March 31. Congress achieved a rare bipartisan breakthrough on replacing and reforming that payment formula earlier this spring, but could not agree on whether or how to finance the $120 billion price tag of eliminating those unsustainable cuts. March is probably too soon for a new Congress to develop bipartisan consensus on an offset, and a six-month punt may set up a more serious Medicare bill for the fall.

A newly installed House Ways and Means Committee Chairman Ryan may try to tie SGR reform to broader Medicare reforms such as consolidating Parts A and B's disparate cost-sharing and move Medicare to a more competitive premium support model. Such a package could move through the Senate under "budget reconciliation" — a parliamentary tactic that requires only a 51-vote majority, so long as the provisions have a fiscal impact.

But don't necessarily expect bold action from Senate Republicans in 2015. Republicans will be defending 23 seats in 2016 and wary about exposing vulnerable members to controversial votes that can be demagogued as "ending Medicare as we know it." Many of these seats will be in Democrat-leaning states such as Pennsylvania, Illinois, and Maine. Moreover, several sitting Republican senators will be running for president (e.g. Cruz, Paul, and Rubio) and have more interest in laying out an agenda for the 2016 election than bipartisan lawmaking with the current president.

Perhaps a more interesting conundrum will be how a Republican Congress reacts to an imminent Supreme Court decision, which may prohibit premium subsidies flowing to individuals who enrolled in health insurance through the Federal Exchange. Earlier this year, three federal courts issued conflicting opinions on whether the statutory language providing subsidies for "an exchange established by the State" permits the IRS to funnel subsidies to the vast majority of Americans living in the 36 states that refused to establish state



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"Perhaps Republicans could find common ground with a president who may be more interested in building a legacy than appeasing his base."

exchanges. Those individuals obtained coverage in the federal exchange through the portal, infamously inoperable for weeks, known as Healthcare.gov. Several other states, including Nevada and Oregon, are presently abandoning their dysfunctional state exchanges and enrolling their residents in the federal exchange.

The September U.S. District Court ruling for *Pruitt v. Burwell,* invalidating subsidies in the federal exchanges, is important because it establishes another split in the lower courts and may prompt the high court to take a closer look at the case and consider whether to take it up immediately or wait for pending appeals to conclude.

Federal Judge Ronald White, who issued the *Pruitt* ruling, dismissed political arguments in the previous cases, stating "This is a case of statutory interpretation. The text is what it is, no matter which side benefits. ... Such a case does not 'gut' or 'destroy' anything. On the contrary, the court is upholding the act as written. Congress is free to amend the ACA to provide tax credits in both state and federal exchanges, if that is the legislative will."

Would Chief Justice Roberts hold a similar view that clear language means something? Or would he contort language to divine legislative intent just as he did in his landmark decision upholding the constitutionality of the individual mandate, where he deemed the word "penalty," which appeared 27 times in the Affordable Care Act statute, actually meant "tax?" Who knows?

But a Supreme Court decision that upholds *Pruitt* lands the issue squarely in the Republicans' lap. How do they respond?

Republicans would likely be unwilling to amend the Affordable Care Act to authorize subsidies through the federal exchange. They could make a federalism argument and suggest that each state has the ability to decide whether to establish its own exchange and the subsidies that would flow. But many of those states are the very same conservative strongholds that refused to expand Medicaid even though the federal government was picking up 90 to 100 percent of the tab.

What would be the political fallout of turning the subsidy spigot off for millions of lower and middle income people who finally obtained health insurance coverage? This is precisely why Republicans were fixated on dismantling Obamacare before the subsidized coverage commenced in January 2014. It's always easier to block theoretical benefits than take away tangible benefits people say they currently depend upon. If Republicans do not quickly develop a concrete and coherent alternative to Obamacare, Democrats may finally be able to turn the tables and blame Republicans for taking away coverage that people relied upon.

Perhaps Republicans could find common ground with a president who may be more interested in building a legacy than appeasing his base. Putting Medicare and other entitlements on a more sustainable course requires bipartisan cooperation so neither party can be unfairly maligned. It's an issue House Republicans like Ryan are eager to take up.

But progress also can be made in more incremental fashion. Targeted fixes to the ACA can be foreseen, such as repealing the medical device tax — a measure that has strong bipartisan support. A delay of the individual mandate is a priority for Republicans and yields substantial revenue that could be used for SGR reform or other fixes. It's hard to see how the president maintains his opposition to this penalty, when delays have already been granted to employers. A repeal of the Independent Payment Advisory Board (IPAB) has been a priority for the health industry, because it is empowered to inflict arbitrary and nonreviewable Medicare cuts to healthcare providers and pharmaceuticals alike.

Of course, all of this speculation of a Republican Congress and legislating on simmering health policy problems may be wishful thinking. Many of the Senate races will be decided by a percentage or two, and the final outcome may not be known until January after several states have runoffs. There is still a good chance that Democrats retain control of the Senate (by the slimmest of margins), and the nation grinds through a couple more years of virtual gridlock while we wait for a new president. 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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BEAT BIOTHERAPEUTICS

With what it believes is a breakthrough gene-therapy approach, this early-stage company hopes to shake up the huge heart-failure space.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

BEAT BioTherapeutics, aka BEATBio, believes it has a gene-therapy candidate, BB-R12, that could greatly improve the quality of life for heart-failure (HF) patients. The therapy uses a "humanized construct" or antibody as a vector to induce cardiomyocytes (heart muscle) cells to express an "optimized" form of ribonucleotide reductase, producing dATP (deoxyadenosine triphosphate), a "superior" form of the cellular fuel ATP (adenosine 5'-triphosphate). dATP appears to give an extra boost to the cells and thus improve the heart's performance. BB-R12 is still in preclinical studies, planned for a Phase 1 trial in early 2016. Most of its seed money will fund that trial as well as development of the construct and manufacturing scale-up.

KEY MILESTONES

- Demonstrated that BB-R12 restores ejection fraction and overall cardiac performance in animal models of heart failure and improves contraction and relaxation in healthy and depressed heart muscle cells following injury. No safety issues identified to date.
- Developed and manufactured a humanized gene construct and scaled up manufacturing using a system licensed from the NIH.
- Confirmed earlier rodent experiments using the human construct.
- Completed a successful proof-of-concept study with the humanized construct in a large-animal (swine) myocardial infarction/heart failure model.
- Held a pre-IND meeting with the FDA and confirmed development plans and timeline to enter the clinic in early 2016.

WHAT'S AT STAKE

When a tiny gene-therapy company wants to conquer the heart-failure market, with its patient population of almost 6 million in the U.S. alone, it is only logical to ask some questions. BEATBio is worth watching because it could be an early sign that this long-moribund space, littered with recent failures, is heating up. But the company faces a long haul ahead in proving its treatment can simultaneously deliver strong benefits to millions of patients and meet the challenges of a cost-driven healthcare environment.

At this early stage, the company leaves most of the hard questions unanswered. How practical is gene therapy in such a large population, or will the company target a smaller segment, say, advanced or acute cases only? What will be the likely procedure for the gene therapy — how cumbersome or complicated will it be to treat the cardiac cells?

What clinical efficacy endpoints must the therapy meet for regulatory approval, simply quality of life or survival? Are there practical concerns in the medical care of heart-failure patients, especially older ones, that would limit or affect use of the therapy? The last concern has plagued older HF therapies. For example, infirmity can limit a patient's ability to answer the call of diuretics in the middle of the night. Any medical procedure can challenge such patients.

When I attended BEATBio's presentation at the BIO Investor Forum in October, I asked whether pushing heart cells might exhaust already damaged heart muscles. CEO Michael Kranda's answer was that BB-R12 is "not driving a damaged heart," but using a self-regulating mechanism that boosts healthy-cell performance as needed. Only healthy cardiomyocytes produce dATP as a result.

Of course, in such a large potential space, potential competition is strong. Big Pharma companies have a number of candidates in line for HF. Other small companies, such as Juventas with its stem-cell therapy for advanced HF in Phase 2, are also vying for a place in the space.

May the best MOA (mechanism of action) win, but other factors also count. To its credit, BEATBio has a seasoned team in place. Kranda has both VC and company experience going all the way back to Immunex. The newly hired CMO has been tested by fire; Sam Teichman, M.D., was formerly at Cothera, developer of blood-vessel relaxer serelaxin, which had an application for treating acute heart failure rejected by the FDA last May.

Vital Statistics

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Logistics Providers Strive To Fulfill Biopharma Needs – Specialty Companies Offer Advantages, But Get A Bad Rap On Price

According to clinicaltrials.gov, there are over 92,000 drug or biologic registered studies under way right now. Nearly one-fifth (17 percent) of the drugs currently in development are biologic-based therapeutics.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

> *"It's important to ensure that the logistics company engaged for the job is not the weakest link in the cold chain."*

Because biological assets are temperature sensitive, the challenges in transport and distribution are quite different from logistical obstacles faced by traditional, small molecule-based drugs. Both global logistics giants (such as FedEx and UPS) and a host of specialty logistics companies (such as Marken, World Courier) focused on the life sciences industry have fine-tuned their offerings in order to meet the cold chain needs for biomaterials, such as clinical trial samples, active pharmaceutical ingredients, cell banks, tissue samples, and more.

With high stakes ranging from legal to financial risk, it's important to ensure that the logistics company engaged for the job is not the weakest link in the cold chain. Nice Insight asked 100 respondents in charge of the handling and distribution of biological specimens or clinical trials materials their opinions and preferences on shipping partners. When it comes to overall preference, global logistics companies such as FedEx, UPS, and DHL are favored over specialty companies by a relatively slim margin (39 vs. 31 percent). Thirty percent of respondents stated they prefer to use a mix of both specialty and global logistic companies. Among the group of respondents who use both types of providers, specialized providers received a little more of their business (55 vs. 45 percent).

Respondents attribute on-time delivery and flexibility in pickup and drop-off times to both types of providers. However, logistics giants are best known for their convenience and affordability, while specialty providers are associated with temperature-control options and white-glove handling. Because participants indicated they are more likely to select a logistics company based on best fit for a project rather than price, the added-value services available through specialty providers are likely to win the companies' new business. And — based on 97 percent of respondents who said their logistics expenditure increased or stayed the same last year — there is more business to be had. Only 3 percent thought it would decrease.

Real-time traceability for shipments (63 percent) along with logistical locations (56 percent) and regulatory expertise (54 percent) are the leading reasons for engaging a third party logistics provider for handling biomaterials. Twenty-four/seven customer service topped the list of the most sought after technologies and/or services from logistics providers.

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FIGURE 1 Strategic Motivations For Engaging Third Party Logistics Providers

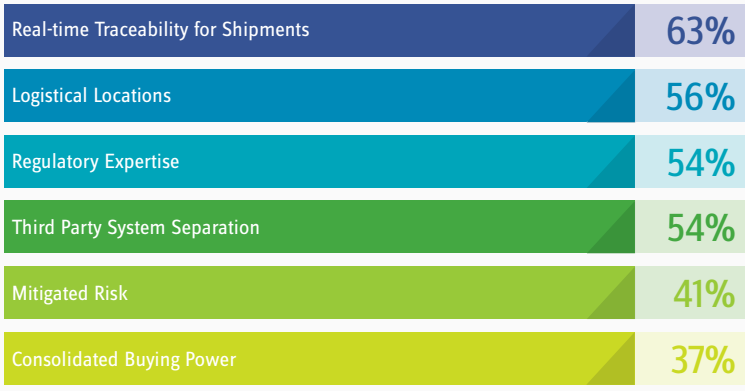
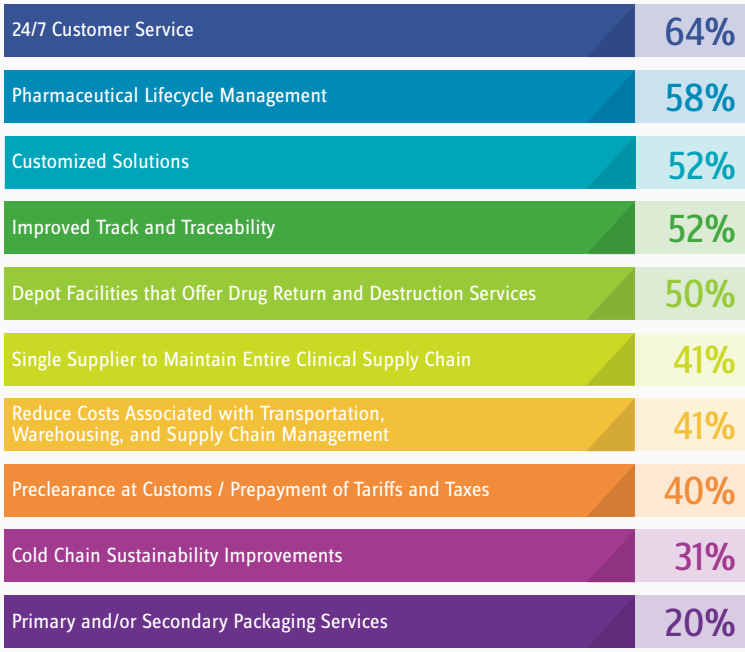


FIGURE 2 Desired Technologies And Services In Logistics Providers



Survey Methodology: Nice Insight conducted a supply chain survey targeting 100 supply chain decision makers. The survey was comprised of 30 questions geared toward understanding current supply chain needs and practices, present and future expectations from logistics providers, and which services and traits influence provider selection.

Customer service is followed by more specialized services such as pharmaceutical lifecycle management, where storage, distribution, and reverse logistics are all handled by the provider — an area where a specialty company has a clear advantage. Depot facilities that offer drug return and destruction services, as well as retest labeling for clinical trials materials, are additional areas where biopharma companies desire solutions that specialty companies are best positioned to fulfill.

It's not surprising that logistics giants are perceived to be more affordable than specialty providers, or that price ranked fourth in importance, after quality, reliability, and regulatory knowledge. Both of these statements — along with 49 percent of respondents stating they "select a logistics provider based on project best fit" when asked about pricing tolerance — support use of a combination of global and specialty providers. Thus, it is interesting and somewhat conflicting to see that price came in as the top reason buyers would consider switching from their current supplier.

While global companies continue to fine-tune their offerings in order to remain top of mind among customers in the life sciences market, it will be interesting to see whether these companies are able to develop the same quality of service for life sciences' specialized needs and keep their reputation for being more affordable. L

N. WALKER

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, or Kate Hammeke, director of marketing intelligence, at Nice Insight by sending an email to nigel@thatsnice.com or kate.h@thatsnice.com.

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The Biosimilars Opportunity: 4 Years Of Waiting

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

Biosimilars have been approvable in the U.S. since the 2010 passage of biosimilars-enabling legislation. However, no product applications have been approved. A few have been filed, but the industry largely remains on hold as the FDA waits to release needed guidance. Now, even the U.S. Senate is pushing the FDA to release guidance documents on biosimilar drug approvals. A group of senators in August wrote the HHS (Department of Health and Human Services) about the implementation of the Biologics Price Competition and Innovation Act (BPCIA), enacted to push the FDA to develop a framework to review and approve biosimilars. This delay has heightened concerns about just exactly how biosimilars will affect patients, insurers, drug companies, and even suppliers.

BioPlan has evaluated this industry for over 25 years, and out of the roughly 4,500 biopharmaceutical candidate products in the pipeline, around 20 percent (approximately 900) are follow-on biopharmaceuticals, mostly biosimilars (>500), but also biobetters. In our studies, we outline that only a percentage of these will make it to the market.

Of interest are questions about how expensive biosimilars will be, how they will be marketed, and whether more efficient (cheaper) manufacturing for biosimilars could ultimately improve biomanufacturing for all products. Other unanswered questions include concerns regarding the extent of competition. As new industry entrants emerge, some will be more concerned with getting U.S. approvals than with actual revenues and profits. This may result in disruptive pricing that could affect other areas of biologics as well.

EXPECT MORE SMALLER PLAYERS TO ENTER THE MARKET

There are some undisputed trends accompanying the growth of biosimilars. We can expect many new companies to this industry of all sizes and types — including generic drug and foreign companies. We will find emerging geographies seeking to establish themselves in the mainstream biopharmaceutical industry via a biosimilars route. This will continue as the industry matures and more products come off patent.

For many biosimilar/biobetter developers, profits or capturing market share in major markets such as the U.S. and EU might not be a primary goal. Instead, it's likely that they'll view U.S. product approval — even if just for a biosimilar — as validation, and regulatory acceptance of that product for sales in lesser-regulated markets around the world. These entrants may also see gains in company valuations, after U.S. or EU product approval.

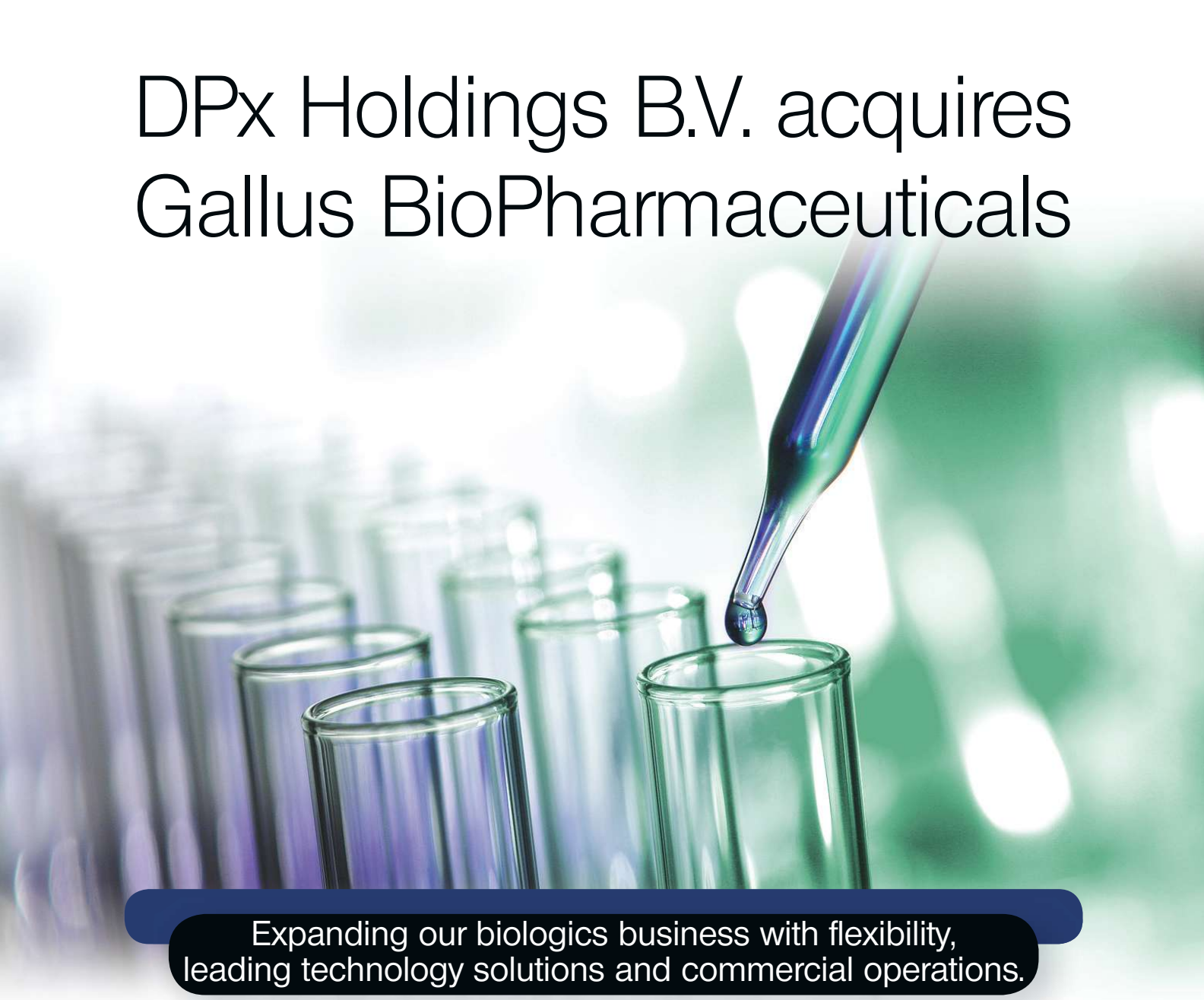
THE U.S. MARKET TAKES SHAPE

The U.S. will most likely still be the dominant biosimilar consumer market. Even compared to the EU, the U.S. has a large population and an insurer base motivated by cheaper biosimilars. It's therefore likely that the U.S. will become very competitive and perhaps overcrowded, as dozens of new and established companies jockey for market share. Profit margins may be driven down as a result. Despite this, the U.S. biosimilars opportunity is attractive. Indeed, as the chart on page 22 shows, biosimilars will soon be able to compete with reference products that boast cumulative annual revenue of roughly $100 billion.

KEY BIOSIMILARS TRENDS

Biosimilars Will Not Expand Product Markets: The number of companies, manufacturing activity, and products that form the follow-on product market will most likely not expand the market's overall value, and may instead contract it. Biopharmaceuticals are a zero-sum market. Making them a little cheaper will not expand their use. Biosimilars will maintain a constant number of units sold, but will reduce the combined sales value for reference products and their biosimilar versions. This overall market tightening (in dollar terms) can readily be seen with generic small molecule drugs, where deeply discounted generic products can capture up to 90 percent market share in a matter of weeks. Biosimilars are expected to be discounted to a lesser degree (≤30 percent) than generics, but a similar market dynamic will likely play out. Expect to see the number of players increase as markets become more fragmented.

DPx Holdings B.V. acquires Gallus BioPharmaceuticals



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- Biosimilars Will Be A Boon For CMOs: CMOs are among the major beneficiaries of the new wave of biosimilars and biobetters, with many already seeing increased demand across a range of activities, from bioprocess development to scale-up and manufacture of preclinical and clinical supplies. Some CMOs are reporting overall business increases of 15 percent due to biosimilars contracts. These opportunities will continue for CMOs. Established drug innovators will prefer to devote limited in-house capacity to newer, higher-profit products. CMOs will manufacture their biosimilars and biobetter products. Analyses contained in our *11th Annual Report and Survey of Biopharmaceutical Manufacturers* suggest that 40 percent or more of biosimilars and biobetters could be manufactured by CMOs.
- The New Wave Of Biosimilars Will Spur Innovation: To remain competitive as biosimilars and biobetters evolve, product developers and manufacturers will need better ways to cut down on time to market and streamline the overall testing process. The industry is demanding higher productivity and lower manufacturing costs, and many players are looking to industry suppliers for the innovations to advance analytical studies, clinical testing, and other technologies needed to support biosimilar approvals and production.
- Cost-Effective Biomanufacturing: Biosimilars developers will need to adopt the most cost-effective manufacturing technologies just to be able to compete. Expect widespread adoption of newer, advanced expression systems and improved disposable upstream and downstream bioprocessing systems. In general, developers are not looking to reverse-engineer and mirror reference products' legacy manufacturing methods developed decades ago. Rather, biosimilars developers are already using some of the newest and most improved bioprocessing methods. These are expected to improve processing and lower manufacturing costs.

SUMMARY

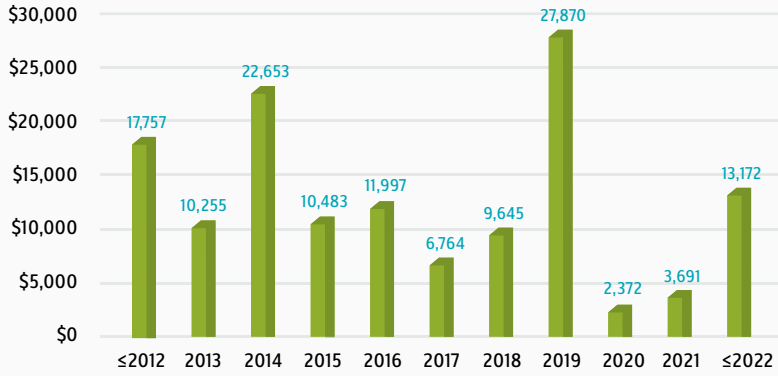
These trends toward production efficiency will also affect manufacturers of future reference products. As better production technologies emerge, they will first improve new biological product manufacturing. That is, advanced bioprocessing technologies will first provide advantages to makers of these newer follow-on products, As such, we can expect biosimilars and biobetters to be factors in the pioneering of many new technologies, such as better analytical methods, improved expression systems, single-use systems, alternatives to Protein A, and other conventional chromatography processing.

In a recent survey among BioPlan's Biotechnology Industry Council™, our 425 global subject matter experts identified the following micro-trends in the biosimilars market:

- Expect more models and analytical methods for demonstrating biosimilarity and biochemical or biophysical characterization;
- Expect more established regulations, definitions, and standards for biosimilars and "biosimilarity";
- Expect bioprocess tweaks allowing for fine-tuning of biosimilars to match innovator biologics; and
- Expect more quality by design (QbD) and design of experiments (DoE) for all products including biosimilars.

To those trends we also add that many current developers face challenges in the short term. Many companies are already far ahead, and the competition will be fierce as many seek to market the same product to a limited pool. Overall, the coming wave of biosimilars and biobetters will bring big changes to the market, enhancing the role of the CMO, expanding the number of players in the global market, and spurring breakthrough new technologies. Our upcoming studies will provide global subject matter review of these trends and their impact on global biopharmaceutical markets. L

FIGURE 1 U.S. Biosimilars Launchable Dates 2012-2013, By Current Reference Product Sales ($Million)

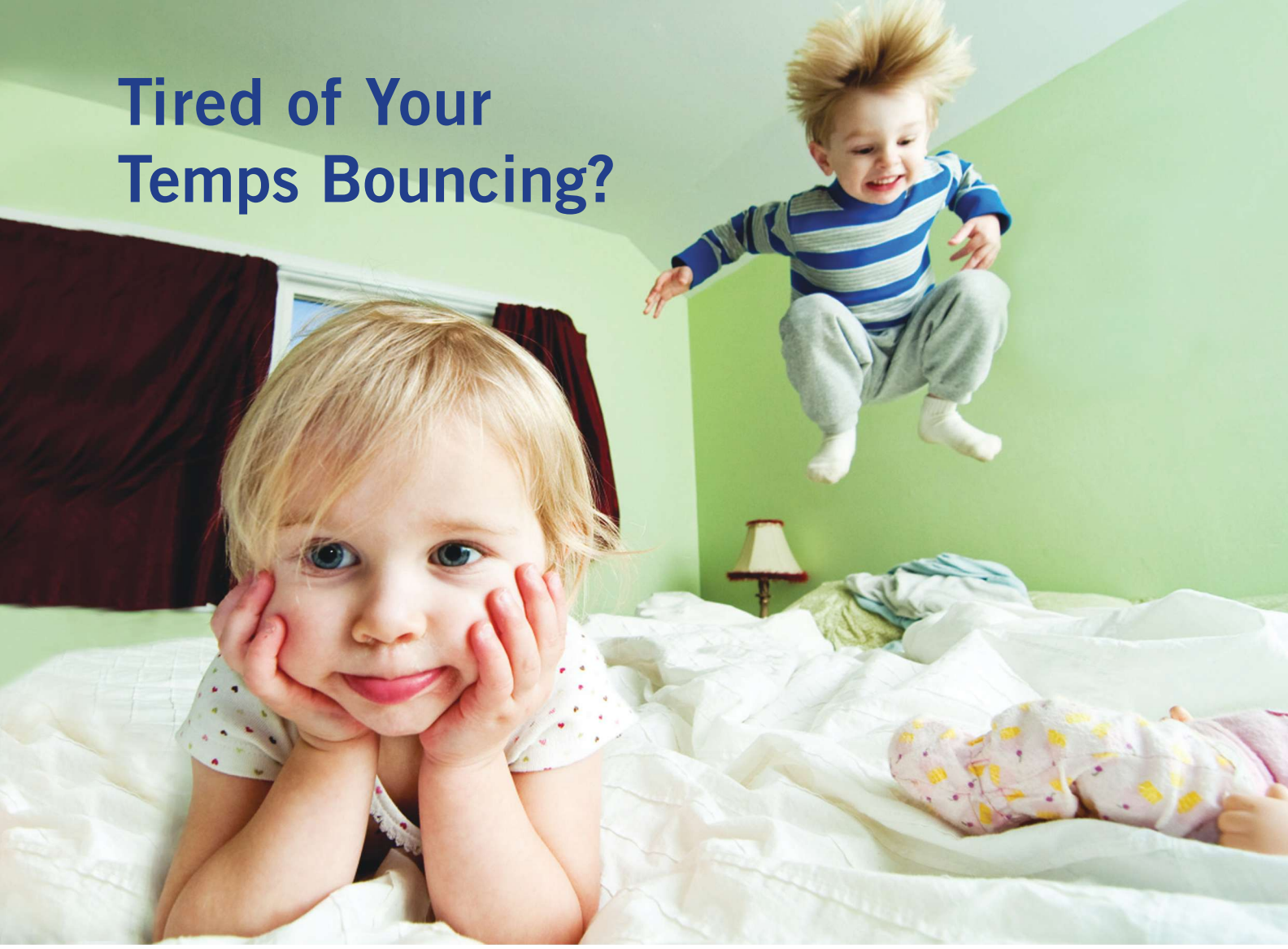


Bars represent the total dollar estimated sales ($millions) by year for all U.S. reference biologics potentially producible as biosimilars. This data implies total market potential for biosimilars, based on when specific U.S. biololgics become available for biosimilar production.

Source: 11th Annual Report and Survey of Biopharmaceutical Manufacturers, April 2014, www.bioplanassociates.com/11th

Survey Methodology: The *2014 Eleventh Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* yields a composite view and trend analysis from 238 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also included over 173 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

Tired of Your Temps Bouncing?



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GLAXOSMITHKLINE

REFOCUSING, RESHAPING ONCOLOGY R&D

WAYNE KOBERSTEIN
Executive Editor

Soon after my first conversations with GlaxoSmithKline about interviewing its head of pharma R&D, the news hit. In a mega-swap of product lines with another global pharma giant, GSK gave up its entire commercial oncology portfolio to Novartis in exchange for the Swiss company's vaccine line; at the same time, the two companies combined their consumer health units into a single business with GSK as the majority owner. Oncology was no small part of its drug division at the time, accounting for about 4 percent (about $1.5 billion) of pharmaceutical revenues before the Novartis deal.

Early on, it took reading past the headlines to grasp GSK's full intentions. Essentially the company is refocusing its oncology R&D, all the while continuing to reshape the entire pharma R&D organization. The leader in charge of the transition is Dr. Patrick Vallance, president of Pharmaceuticals R&D. A former academic researcher, Vallance headed drug discovery before taking on the entire pharma R&D unit in 2012.

Thus he has witnessed the good, bad, and the less-than-pretty results coming from the organization during his eight years with the company. After a comparative dry spell, GSK staged a recovery in drug development in recent years, with six new drugs entering the market since 2012.

The company's bonus program for discovery scientists, giving a small incentive at proof-of-concept and a bigger payment at approval, turned out to be a good surrogate marker for the new-drug surge. "Medicines can fail at any stage, so we didn't want to give big rewards at the end of Phase 2a; we wanted to signal there was a big reward to be given at that point, which would come when the medicine becomes a medicine, and we paid up on that promise with the product approvals," says Vallance.

Those successes, however, have not stopped the R&D transformation already under way — and, in fact, the new products are more reflective of the company's past than predictive of its future direc-

DR. PATRICK VALLANCE President of Pharmaceuticals R&D at GlaxoSmithKline

tion in drug development. All of the recent approvals are in GSK's established market areas, mirroring their relatively broad focus: COPD/asthma, diabetes, HIV, and cancer (melanoma), with the two molecular-pathway targeted drugs in the last category joining the exodus to Novartis. GSK's current pipeline reveals that the company, not unlike most of its competitors, is heading into niche-drug territories, driven and guided by a careful reading of scientific opportunities and the reimbursement landscape.

At the same time, as heralded by Chairman Andrew Witty, GSK will seek to lead the industry in the trend toward sharply reduced R&D budgets, attendant cost-cutting, and collaborations with all sorts of research entities in the quest for biotech-like innovation — without, of course, incurring the usual, though oft-ignored high failure rates of the startup biotech sector. To reduce the risk of duplicating the darker side of entrepreneurial biopharma, the company aims to make the best possible use of its natural assets, the "platforms" of drug discovery, development, and commercialization that only a Big Pharma like GSK can maintain.

REPRODUCIBLE, RESILIENT, AND REAL

It is useful to know how and why Vallance joined the company, because his responsibility ultimately came to encompass both affirmation and optimization of the organization he would head. He was well along in an academic career at University College London, when he met GSK's then head of R&D, Tadataka (Tachi) Yamada, and subsequently answered Yamada's invitation to join the company in May 2006.

"If you'd asked me the day before I decided to move to GSK, I would have said I absolutely had no intention of moving to industry," he recalls. "I was a clinical academic. I saw patients. I ran a big department. I knew my next job would be running the medical school. I had been on the research advisory board for GSK for a couple of years, which was eye-opening for me both scientifically and in the way people thought about treating major medical problems."

After an advisory board meeting in London, Yamada asked Vallance to head GSK's drug discovery. Resisting the offer at first, Vallance later thought, "I could spend the rest of my career doing academic research that might lead to drugs or even, as I was doing at the time, making molecules that interfere with biological processes — or I could go and do the real thing, seeing molecules all the way to becoming medicines. This looked like a really big, interesting career change, and I decided to do it. It was a decision with no great planning or logic behind it and one that I have never regretted for a single second since then."

His initial revelations at the company were mainly positive: "One of the things that struck me was the outstanding quality of the science that goes on and the attention to data reproducibility and integrity, a huge issue in many academic sectors and in the published literature. The dedication to more reproducible assays was very impressive. It was important for me to get to grips with what it means to have robust and reproducible data at this scale of R&D."

Scale itself — the industrial scale of discovery and development activities at the company — also impressed Vallance, and at the same time led him to ponder an inherent conundrum in the large-pharma model. "The number of projects is big, and of course, that's good in one sense. But it leads to a question: What is the depth of understanding underpinning every project?" That thought became his mission: finding a way to increase scientific understanding of drug mechanisms and drug interaction with the human body, so the company might focus on fewer projects in greater depth.

Vallance saw a potential opportunity in the industrial setting to create an advantage that eluded the academic world. At its best, GSK allowed all the different R&D disciplines — chemistry, biology, biopharmaceuticals, and so on — to interact in "an incredibly fluid way," he says. "Getting all of those elements together to work as an integrated, multidisciplinary team is frankly the dream of a lot of people in academia, but it only seldom works." Again, over time he looked for a way to make the concept even more effective in practice.

During the six years following his move to GSK, Vallance rose from head of drug discovery to senior vice president of medicines discovery and development, helping plan and implement the first major R&D reforms driven by Witty and Moncef Slaoui, now chairman, Global R&D & Vaccines. Those reforms began in discovery, involving the creation in 2008 of about 40 teams, consisting of 40 to 60 members, called Discovery Performance Units (DPUs), out of the six former disease-area units. The DPUs were designed to integrate disciplines even more effectively than did the preexisting company culture. They were also to echo a new "open-research" philosophy of external collaboration, by re-creating start-up-style innovation internally.

When Vallance was appointed head of Pharmaceuticals R&D in January 2012, he continued to lead reforms reaching past discovery through all the stages of drug development. But in addition to the internal restructuring, GSK also began a campaign to shift much of the R&D burden and risk to a massive external network of companies and institutions. Overall, Vallance believes the organizational changes have reinforced a more bottom-up, scientifically driven approach to new drug development, moving the company away from the old top-down,

> "We had to reintroduce personal accountability and individual leadership."
>
> **DR. PATRICK VALLANCE**
> President of Pharmaceuticals R&D
> GlaxoSmithKline

market-driven paradigm that held sway for so long in the industry.

"We now have the freedom to discover on the basis of science, which makes it possible to make surprising new discoveries rather than the ones we wished and expected to discover. You have to build new medicines from what is scientifically credible, rather than go where you see simply a big market. Of course, the scientific line must be linked to a vision of patient need, but if you are completely focused on the market from day one, you close things down — and if you start by aiming at where you see the biggest dollar sign, you will end up in a weird place scientifically and medically."

THE TRACK OF CHANGES

As the mechanics of GSK's R&D reorganization continued to evolve, all the related efforts conformed to the two key principles employed by the DPUs, according to Vallance — personal accountability and openness to external collaboration. Both principles were reflected in progressive structural changes.

"We had to reintroduce personal accountability and individual leadership so that we didn't end up with everything being a total team effort and nobody really taking accountability for projects," he says. Personal accountability called for smaller, integrated teams. It was not always as painless as it sounds. Teams that underperformed were cut, with their funds, and often their personnel shifted to new teams. Some long-term people prospered; others found themselves demoted or worse.

With the startup of the DPUs, the company eliminated some therapeutic areas in R&D, such as some late-stage neuroscience work, and reportedly made around 3,000 R&D-related job cuts worldwide. Besides respiratory, the company's largest market area, GSK's current pharmaceutical pipeline lists candidates in oncology, respiratory, cardiovascular/metabolic, immuno-inflammation, infectious diseases, ophthalmology, neuroscience, and various rare diseases. DPUs are also subject to periodic pruning. In 2012, following a review of all DPUs, the company cut

LYNN MARKS: ACCELERATING GSK'S R&D INNOVATION

Reporting to Patrick Vallance, GSK's head of pharma R&D, Lynn Marks is a senior vice-president in charge of a group called Projects Clinical Platforms and Sciences (PCPS). His group's responsibilities cover the conduct of all of the Pharma R&D Phase 1 through Phase 4 clinical trials, with rare exceptions. PCPS has a staff in more than 40 countries and is one of the company's "platform" organizations. In addition to clinical trial operations, its functions include business IT support provided by a PCPS subgroup, Business Planning and Performance. In parallel to PCPS, a closely related nonclinical platform group covers clinical trials drug formulation and supply. Marks also sponsors the company's "Simplifying Clinical Development Change Initiative" and is corporate secretary for TransCelerate Biopharma, the trans-company collaboration to improve efficiency and productivity in clinical development.

"All of the companies in this industry realized five to 10 years ago that they were spending way too much money for the deliverables of a new medicine launched into the world," says Marks. "All the change initiatives that companies did — we called ours Simplifying Clinical Development — was to look at ways to reduce costs, increase quality, boost efficiency, and simplify the processes across clinical development. So we put our program in place about five years ago, and we have tracked the magnitude of savings and monitor the quality of our trials."

Having accomplished its mission, with projected savings of "hundreds of millions of pounds across that time frame," the initiative comes to an end later this year. But Marks says initiatives such as Simplifying Clinical Development also helped spark the thinking that led Global R&D Chief Moncef Slaoui, along with Patrick Vallance and other industry R&D leaders, to begin building what turned out to be TransCelerate Biopharma — and attract 18 other, mainly midsize and large pharma companies into the not-for-profit collaboration to date. Marks worked with R&D executives from other companies to get TransCelerate up and running, initially chaired the operations committee, and now serves as secretary of the organization.

"Dr. Slaoui was very keen on the idea that we could work in collaboration in a precompetitive way on how to increase quality, decrease costs, and increase efficiency in the clinical development space. So I was brought in very early in those conversations in regard to how my organization could participate," he says.

One area TransCelerate took on was data standards, with CDISC, a dictionary of terms associated with therapeutic standards that all member companies use when they report their information into regulatory agencies. The member companies have since put additional resources into CDISC to accelerate the development of therapeutic standards, according to Vallance. "Our goal was '55 in Five,' or introducing 55 new therapeutic area standards in five years. We didn't want to re-create something that was already in place but rather get our resources aligned and make clinical development move faster and more efficiently."

The obvious and oft-asked question about TransCelerate is why collaborate with a set of companies that are otherwise competitors in the industry? Marks describes the dynamics of collaboration. "We are fiercely competitive, and we have to be ever-conscious of anti-trust issues, so we make sure we're clear of all that by having active involvement from our colleagues in Legal. We look for areas where we want to advance something and believe, as a group, if we work together, we can actually advance it faster. Good clinical practice training was one example in which we could make the lives of our investigators around the world simpler. We decided to train them with an agreed set of fundamentals on good clinical practices, which each of us would have done independently and redundantly in the past." TransCelerate is also working to build an electronic portal through which all 19 companies would communicate with investigators globally.

Comparator drugs for clinical research is another area the group took on — to the surprise of doubters, Marks adds. "In the old world, if we wanted to run a clinical trial using another company's marketed product, we would often go through a third party that would buy it in various countries and ship it to us. Now we have multiple agreements among companies to buy directly from each other, so we know the pedigree and the characteristics of the product and can ensure a high-quality, reliable source of the clinical trial material. I am particularly proud of the team for this because many people thought we couldn't do it."

This industry "League of Nations" gives new meaning to the popular term "partnering." No longer is a partner just a license holder or trusted supplier; now the term may apply to a lengthening list of collaborations, including the "precompetitive" tide that lifts all boats.

"The space of where we can go is only limited by our imagination and our appetite for precompetitive collaboration as an industry," Marks says. As an infectious disease specialist, he sees antibacterials as a key example that such cooperation can have a big impact. "It is one of those areas in which we will have to call on the collective leadership of government, academia, and industry, and we will have to break down the barriers across companies to improve our response to the growing threat of antimicrobial resistance. How can we advance that kind of collaboration across the industry collectively?"

three of the units, reduced funding on five, and raised funding on six.

Thus, it is apparent DPUs compete for budgets and must manage their finances like an independent company. They are judged on their outputs by a panel that includes external advisers as well as internal experts from R&D. "The change to DPUs has been an extremely successful path for us," says Vallance. "It has created what I call integrated drug discovery. When I joined GSK, most discovery people were either running a chemistry line, a biology line, or a clinical development project. What the DPUs have done is create individuals who run virtual biotechs. The units have been very successful in the integration of disciplines and progression of projects in a focused way, rather than a reliance on the volume or number of projects."

Receiving the nascent medicines from the DPUs are Medicines Development Teams (MDTs), which take responsibility for getting the surviving product candidates through late-stage development. Even smaller than the DPUs, the MDTs each own an individual project in the late-stage pipeline with "a lot of accountability, a lot of ability to do things the way they want to do them, and a lot of team responsibility for results," Vallance says.

On an even wider scale than the internal reorganization, the externalization of research has brought extensive restructuring affecting several thousand more jobs and careers. The company saw the strategic changes as necessary to break the ice jam holding back pharma R&D productivity for GSK specifically and the industry in general — in any case, forcing the large companies to obtain most of their winning new drugs from the entrepreneurial sector. "Underpinning everything are strategies to diversify through business development and increasingly through links in academia," says Vallance.

In Vallance's view, the final leaf in the table, ace in the hole, winning play, or what-have-you is the leverage of using the unique platforms a Big Pharma brings to the table — small molecule and/or biopharmaceutical production, clinical trials management in multiple countries, a high-quality regulatory organization, reimbursement planning, and other resources tasked with supporting the small R&D units. "The platforms exist to support the projects and not the other way around," he says with emphasis, highlighting a role reversal from the industry's traditional platforms-drive-research paradigm.

A NEW FOCUS ON ONCOLOGY

Six years into GSK's R&D restructuring, another earthshaking change now comes to challenge, or perhaps liberate, the organization. As proposed, the Novartis deal redraws the landscape of therapeutic areas and destinations in GSK's pipeline. As of press time, the regulatory process is still unfolding and it is too soon to describe the agreement as final, but the general outlines are clear: GSK's vaccine business, separate from the pharma unit, will of course grow larger, but the entire commercial line of cancer drugs will go to the other company.

Aside from the corporate impacts on critical mass and market portfolios, the deal's effects on R&D may be dramatic. In oncology, the organization will no longer focus on postmarket development but must realign to an early development, pioneering mode in epigenetics and immuno-oncology. Why does the company want to abandon even a nominally successful product line to chase after therapeutic approaches still as unproven as they are far-reaching?

Vallance explains that, despite having a good track record in oncology discovery, GSK ranked only about 15 in cancer drug sales, and though it might aspire to the top 10, it would likely never reach 1 or 2. Moreover, the drugs the company had commercialized would continue to demand more and more support with expensive postmarketing studies.

"The deal allows us to go back and focus on the earlier areas that have excited us, epigenetics and immuno-oncology, to make sure that we really invest in those properly. If all goes well, they will become anchor areas for the next wave of products in the pipeline, which at some point will take us back into oncology commercially or make us partner of choice for Novartis or another company."

He says the oncology situation illustrates another principle that Andrew Witty has advocated: "We will discover what we discover, and we will develop the medicines we want to develop. We won't always be the right company to commercialize a product, but we must be sure to apply our focus and our size appropriately." Such a flexible strategy seems well-suited to the small-team, entrepreneurial approach of DPUs and MDTs, where risk may be more quickly recognized and, hopefully, mitigated.

So is GSK starting over in a totally different way with oncology? "That is exactly what we are doing," Vallance replies. "Immuno-oncology and epigenetics are likely to require greatly different development tools and a different way of thinking about development, and exploring the new areas gives us an opportunity to do just that. Increasingly, one gets drawn into more and more combinations of therapeutics with a variation of MOAs (mechanisms of action). This gives us a chance to rethink things. No one knows yet exactly how to develop an immunotherapy or epigenetics drug. We don't even know yet how we should be thinking about the ways to deliver the drugs, what the safety profiles should be, and so on. All of it will require a whole new look at the organization."

Some of the products in GSK's pipeline may initially target rare diseases or narrow indications, yet turn out to be applicable to much broader treatments. In immuno-oncology, certain MOAs now in testing seem to work equally well in many different kinds of common tumors as conventionally defined, by organ. (See also Part 3 of "Combination Cancer Immunotherapy — A Virtual Roundtable," on page 36.)

Vallance gives an example in another area, an ex-vivo stem-cell/gene therapy in Phase 3 for a rare, fatal childhood disease called adenosine deaminase severe combined immunodeficiency (ADA-SCID). Although the disease is extremely rare, the therapeutic mode has far-reaching implications, he says. "Cell/gene therapy is where we need to be because it allows us to really understand how to apply a new technology. We may ultimately have broader

applications to much more common diseases. That's exactly the question going on at the moment in oncology, and it places an emphasis on epigenetics — whether immunotherapies will also become fragmented as we realize that patient populations respond very differently depending on their epigenetic profile."

If by some circumstance the Novartis deal does not play out as planned, GSK's intentions in oncology will be nonetheless revealed. It will, by one measure or another, pivot its R&D focus from older cancer drugs and MOAs to the cutting edge of cancer therapy, based on the solid, but always shifting, ground of scientific understanding.

DISTRIBUTING RESEARCH

One aspect of R&D the Novartis deal does not change, at least in direction, is GSK's externalization strategy. To the extent that the pharma R&D organization feeds the Rx-to-OTC pipeline, it will gain global scale and strength from the ex-Novartis consumer business. But the deal will not impede the growth of GSK's worldwide collaborations with companies and academics. Other initiatives, such as the Oncology Clinical and Translational Consortium (OCTC), an international, collaborative research network of six major cancer centers, will also continue unabated. (See "Lynn Marks: Accelerating GSK's R&D Innovation" on page 27.)

Summed up, the combination of entrepreneurial internal teams and external partners builds on a distributed research model. "What we won't do is build more brick-and-mortar innovation centers across the globe. But we are forging strong alliances with biotech and, all importantly, with academia worldwide. We have some interesting ways of attracting academics leading research in our areas of interest."

Discovery Partnerships in Academia (DPAc) is a global program that builds virtual companies around selected ideas submitted by academic scientists or labs based on preclinical or early clinical results. "We place a senior drug discoverer from GSK with the academic, agree that together we will make a medicine, and the whole thing is milestone-driven. They get the keys to GSK, they get a top-class team on their project, and they can publish everything." If a project must end because of technical roadblocks, the academic partners can keep the data and continue to work on the idea with another academic or company partner.

"The DPAc program has formed a series of virtual biotechs across the globe, the most advanced of which is now in Phase 3, and it has worked really well as a system," Vallance attests. "We now have an office in San Diego where we're forming more such alliances. We've done partnerships with groups like Avalon Ventures to create new venture partnerships with academics, and we have opened a new space in Boston. The program is about making links with academics rather than putting up big new laboratories. In fact, we believe that the brick-and-mortar facilities tend to end up being fortresses rather than places where true collaborations occur."

LONG ROAD, STEADY CLIMB

GSK has now traveled quite a distance in reforming the R&D organization — far enough, in fact, to have tracked and measured the payoff in improved performance. Every year, the group publishes its internal rate of return, comparing it to a target rate of 14 percent. The rate has climbed about one percentage point per year since 2010 to reach 13 percent in 2013. The period fairly well conforms to the time when most of the reforms took effect while sales fell, so, objectively, the evidence suggests the reorganization is working.

The company appears to be alone in revealing its return on R&D. In an industry dominated these days by real-time stock trading, the multiyear measurement alone may set GSK apart from its market-jittery peers.

"One of the principles that is critical for R&D is to stay true to an approach long term," says Vallance. "The tendency to change bets every couple of years in a business where it takes 10 years or 15 years to develop a drug is terribly counterproductive, so we are very happy with the overall structure we have built and with the way the returns are going, looking long term. I believe we'll stay with that strategic approach."

> "Medicines can fail at any stage, so we didn't want to give big rewards at the end of Phase 2a; we wanted to signal there was a big reward to be given at that point, which would come when the medicine becomes a medicine."
>
> **DR. PATRICK VALLANCE**
> President of Pharmaceuticals R&D
> GlaxoSmithKline

Many years ago, a young writer/editor waited for hours in a hot room outside the chairman's London office. The company was Wellcome; the chairman, Sir Alfred Shepperd. On another day, the same journalist sat in SmithKline Beecham's London-suburb headquarters speaking with CEO Jan Leschly, and on another, in North Carolina's Research Triangle Park with Ernst Mario, CEO of Glaxo. All of those companies and more became the components melded into GlaxoSmithKline over a long journey of many steps.

GSK faces another long road ahead as it continues to tweak and put its new R&D structure to the test. Execution will prove more important than theory. At every level of implementation, from the DPUs to the partners and suppliers, the returns will rise or fall on the choices the company and its leaders make with every step.

HOW TO BUILD REAL PATIENT-CENTERED PHARMACEUTICAL COMPANIES

ROB WRIGHT Chief Editor

With such a focus these days on buzzwords such as "patient-centric," "patient-centered," and "patient-centricity," some people are predicting "patient engagement" to be the next big movement in our industry, much as blockbuster drugs were a decade or more ago. But while improving patient engagement sounds fairly straightforward for those who directly interact with patients (e.g., doctors, nurses, nurse practitioners, and physicians assistants), for the biopharmaceutical industry, successfully executing this concept has been — and continues to be — much more challenging.

If achieving patient-centricity is biopharma's Holy Grail, I thought I would seek some insight on this topic from the leadership team of a business built on serving patients. Founded in 2004, PatientsLikeMe, a for-profit company built on the principle of patient engagement, has grown from a single online community for ALS patients to a business covering 2,300 health conditions gathering real-time data from 300,000 members.

In the company's bustling, brownstone headquarters in Cambridge, MA, I was joined by Jamie Heywood, cofounder and chairman; Ben Heywood, cofounder and president; and Martin Coulter, CEO. Together, they shared with me their perspectives on why biopharma companies struggle when it comes to engaging with patients, as well as what companies can do to become more patient-centered.

WHY DOES PHARMA STRUGGLE WHEN SEEKING TO ENGAGE PATIENTS?

While being highly regulated or culturally conservative are most likely contributing factors to biopharma's patient-engagement struggles, to understand being patient-centered as a strategic solution, the PatientsLikeMe execs suggest you go to the root of the problem — the deeply infused cultural rules of clinical research.

> "As that world changes and the physician channel is going away, there's this realization of needing to develop a different model for establishing a relationship with patients."

MARTIN COULTER
CEO of PatientsLikeMe

"As you're talking to people about how to do clinical research," Jamie Heywood analogizes, "it is as if Moses came down from Mount Sinai with a third tablet that said, 'Thou shalt only do a double-blind placebo-controlled trial and believe only the evidence from that.'" This mentality creates a number of problems. "The purpose of blinding a study is to eliminate biases," he shares. "Because blinding is the only approach many researchers have ever known, and, therefore, the only evidence which they will ever believe, they are less open to considering new ways of conducting clinical research." For example, PatientsLikeMe has developed an ALS predictive model that Jamie says is so accurate it is conceivable to conduct a clinical trial without a placebo. "It's now been validated in multiple publications," he states. "If you can determine whether a drug makes a difference against prediction instead of placebo, this is really neat because you can do what might be an 80- or 100-person trial with just 25 or 30 people. That's dramatic cost savings and you can do more dose ranges for the same money." Jamie believes that being able to conduct a clinical trial against prediction versus placebo could not only be cheaper but also better and faster to market. Though the rules of clinical drug trials are constantly being revised and rewritten, testing against prediction is not considered a viable option. Patients desperate for solutions are willing to try just about anything. As such, they want researchers open to trying new solutions, not ones blinded by their own biases.

Although the PatientsLikeMe team admits the present way in which clinical trials are conducted is adequate for the purpose of getting a drug approved, they contend it is not at all patient-centered. "Medicine and clinical research are very paternalistic fields that have largely regarded patients as subjects which perform best when they are adherent, compliant, unquestioning followers of the rules," says Jamie. This attitude is not conducive to creating a relationship between patient and researcher, and subsequently, patient and biopharma. To achieve patient-centricity requires creating a relationship where the patient is an equal partner similar to your other business partnerships. "In a partnership with a biotech or a clinical research company, you're not sitting there at the end, saying, 'Hey, you patient, help me out here so I can make this medicine that makes your disease better that you may or may not be able to buy from me in the future,'" says Jamie. "That's not a partnership. That's a subject relationship."

Another reason why biopharma has struggled with patient engagement is that the industry has relied on one-way communication that often includes only mass media and the healthcare provider. "As that world changes and the physician channel is going away, there's this realization of needing to develop a different model for establishing a relationship with patients," says Coulter. "But there's a lack of infrastructure, experience, and understanding as to how to do this effectively." Ben Heywood adds, "The first instinct

The Disappointment Of Clinical Outsourcing

Jamie Heywood, the cofounder and chairman of PatientsLikeMe, is disappointed with how clinical trials are outsourced today. He says that although CROs have done a great job optimizing the processes surrounding trials, the sponsors have done little more than tweak some of the parameters that have always been in place. "We've basically committed to a trial model that was designed 20 years ago, outsourced everything according to that model's specifications, and then built an entire optimization system to drive down costs. But during all of this, we've stopped thinking about what a trial is for."

Heywood believes patients and diseases need "continuous measurement improvement." "Pharma needs to enable continual collection of increasingly meaningful information about patient experiences. Doing so will help improve measurement and drive better decision making," he says. He also believes pharma should invest accordingly. "If you're not spending significantly to optimize how you measure a disease, then don't complain about the billion-dollar price tag of drug development," he comments. Instead, broadly engage as partners with the patient community so you can collaboratively improve measures, target patients more effectively, and ultimately reduce clinical trial costs.

of the patient-centered tactic is to invite a patient to 'the table' — to a conference or to an ad board." While this is a big step, the PatientsLikeMe team cautions to avoid the temptation of racing to create a solution to your patient-engagement problem before thoroughly considering the various challenges and how best to overcome them.

DON'T LEAP BEFORE YOU LOOK

One of the most basic challenges when engaging with patients is, "How does a human being know what to do in an information age?" asks Jamie. "The question can be as simple as for the headache I have right now, 'What's the best way to treat it?' Even though these drugs have been used by hundreds of billions of people, we have no idea what the answer to that question is." According to Jamie, there is a limit to the number of variables a human, as a heuristic engine, can process to reach an effective conclusion. In other words, before you invite patients to the table, understand the questions you need to ask them so you are collecting the right data. For example, consider the proxy measures of healthcare, which look at readmission rates or hospital acquired infections. "The core measures are falls or bedsores," says Coulter. "These don't really get to the nature of the underlying condition." If you want to better understand the outcome, start by measuring the experience of the process that led the patient to the outcome. Regarding clinical trials, Ben adds, "Patient reported outcome [PRO] measures are typically designed in the context of doing research and understanding an end point, as opposed to having a patient-centered view of an enabling self-measurement and self-disease management." If you want to develop better end points, you need to meet the challenge of understanding what matters to the patient during their disease journey.

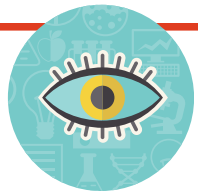
Another challenge to consider is that consumers are increasingly looking for, and have been given, control in their lives. "From how we order a taxi to how we reserve our next hotel stay, consumers are increasingly looking for data, referrals, and input from the crowd," says Coulter. But during or after the clinical trial, participants aren't usually given much access to the data. According to Jamie, "In the highly regimented and rigorous field of clinical research, your currency is building a population of patients, separating them into two different groups, conducting research, and collecting data from which you can then publish articles." As data and publication are what clinical researchers perceive as valuable, Jamie believes this encourages researchers to

only want to share conclusions and not the data from which they were derived. The challenge is not only creating a willingness to exchange data but also making that data digestible for patients. "This requires organizations to be able to figure out not only what's important to patients, but also how to present the findings in terms that resonate with them," says Coulter. "That's a skill the life sciences industry needs to develop."

An additional challenge is the traditional lengthy cycle times of research projects. "Patient-engagement research projects with six-month answer cycles are often overdesigned to produce precise answers," says Jamie. He suggests if you want to start operating your business where you're making decisions in days and weeks instead of bi-annually, retrain your operational directors and vice presidents to seek outside resources which can help operationalize a real-time engagement model and stop overdesigning questions. While adopting a patient-centered approach may make sense, expect resistance at various levels. For example, implementing a patient-engagement approach across a company's therapeutic portfolio (e.g., oncology) might meet resistance from individuals responsible for a single asset (i.e., experimental treatment) within the therapeutic category, especially if input adds new information that they fear could add risk to the asset's success. A further challenge is operating in the clinical research world as it exists while trying to think about, and invest in, how you want it to look in the future. "Essentially, there is no funding, no model, and no mechanism for continually improving the measurement of disease via patient engagement," Jamie says. "At some point in the future, devices around us will monitor enough of our lives that the idea of surveys will be gone. While Jawbone [wrist band fitness activity tracker] as a tool for measuring mobility in multiple sclerosis patients as a changed measurement methodology in a trial is not validated and ready today, at some point it will be." Jamie refers to the time period between now and eventual validation of personal activity tracking devices for use in clinical trials as an inflection point. Though he believes these devices will save therapeutic development companies hundreds of millions of dollars in the future, the benefits and savings will go to only those leaders willing to invest in understanding which of these technologies, and in which contexts, matter. "Leaders need to be willing to invest in these and other inflection points." Ben says transitioning a new concept, such as patient engagement, from the innovation group to operations is challenging. "Demonstrating the value and getting operational buy-in is possible as long as the budget to pay for it is coming from innovation," he states. "What we have seen is the traditional approach of easing it into the operating budget with the initiative being partially funded by both groups." While this sometimes works during the transition, it often fails when operations has full financial responsibility. He suggests if adopting a patient-centered strategy, be sure to consider how to fund it, including creating transition budgets and teams to help the initiative move successfully from an innovative experiment to an operational best practice.

TRANSFORMING TO PATIENT-CENTERED REQUIRES TRANSFORMATIVE LEADERSHIP

Jamie Heywood believes truly transformative businesses were not necessarily built on the idea of being a business. "They were built on a mission that became a business," he attests. "Google did not have a revenue model when it was invented and began to understand how to measure the Web. There were other search engines operating on more traditional heuristics about how to understand things. The parallel to adopting a patient-centered approach at your company is looking at the actual patient experience as essentially the deterministic value of healthcare delivery or drug development." While he believes the Framingham Heart Study and the Nurse's Health Study to be excellent examples of this concept in action, it's not broadly accepted. "We've seen, depressingly, examples where we've delivered transformative levels of value to one franchise team, and that team has tried to bring that same value to other parts of the organization. But the organization goes through the same resistance curve because it just replicates the problem in a different silo. Convincing the pharmaceutical busi-



Patient-Centered Requires Big-Picture Thinking

Idiopathic pulmonary fibrosis, IPF, is about to receive a big cash infusion. "There are now six companies specializing in IPF that are either in or going toward a phase 3 program," says PatientsLikeMe chairman and cofounder Jamie Heywood. A rough number of $200 million each equates to $1.2 billion in spending. One of the problems Heywood envisions is that these six companies are spending more money than they should. Unlike diseases such as ALS, which has an extremely strong clinical trial network, IPF does not. "It doesn't have a network of clinics," he says. "It doesn't have an outcome measure that is accepted or used by the FDA to approve a drug. The current measure, forced vital capacity, doesn't really match the decline of the disease — and the vast majority of IPF patients do not participate in clinical research." Heywood believes these are all fixable problems. "You can build an open clinical research network that is patient-centered and recruit most of the people with the disease. You can educate patients and develop the measures, deploy them clinically, and validate." Instead of operating in isolation, these companies should do some big-picture thinking about how to best help the patient, and he believes all will benefit. "Imagine if the companies pooled $50 million toward solving the various problems around conducting IPF research," he ponders. "Suddenly, you could take a $1.2-billion cost and halve it."

Heywood feels that becoming truly patient-centered requires biopharma to take on big-picture collaborative thinking. "This type of approach would result in getting faster and better signal detection, a better regulatory response, and a far better patient experience," he attests. "Further, because you're integrating trial level measurement into the care process, you can eliminate most phase 4s; risk management is automatic, and as an added benefit you get real-world comparative effectiveness."

ness to think about developing a relationship with the customer/patient requires transformative leadership. "Even with a biopharma company that has 25,000 to 50,000 employees, there are really only about 100 people in those enterprises capable of changing the way a decision is made." To assist you in becoming patient-centered, he advises bringing in change management experts to help.

Transformative leaders need to approach partnering with patients as, "I'm going to solve some problems for you the patient that may or may not directly address our company's needs right now," says Jamie. "And, I'm going to make sure that I enable an infrastructure so that you the patient are better at solving your own problems through this partnership." He analogizes it as being the opposite approach to the bygone days of coal mining. "When a coal company came into a town, tore off the top of a mountain, and left a bunch of chemicals in the streams, even though they'd given everyone a job for a little while, they've left the town worse off." Instead, strive to create a system that leaves the patients better off. "I was at a discussion yesterday with a major pharma about a research project," he shares as an example of what patient-centered is not. "They were really excited about how they did this and that, and said, 'We're being so patient-centric.' I said, 'Really? What did the patients get out of it?' The answer was, 'Oh, they're excited about participating in research, so we make them feel better, because they're participating in research.'" If you want to be patient-centered, ask yourself, "What's in it for the patient? How will you leave them better off? What can you give them to help them organize on their own? Does that data need to be competitive or can it be collaborative? How can you make it available? These are things conspicuously absent in many industry approaches to developing a relationship with patients."

"Medicine and clinical research are very paternalistic fields that have largely regarded patients as subjects which perform best when they are adherent, compliant, unquestioning followers of the rules."

JAMIE HEYWOOD
Cofounder and Chairman of PatientsLikeMe

COMBINATION CANCER IMMUNOTHERAPY — A VIRTUAL ROUNDTABLE

A SERIES ON THE CHALLENGES AND OPPORTUNITIES OF USING NEW AGENTS TO RALLY THE IMMUNE SYSTEM AGAINST CANCER

WAYNE KOBERSTEIN, Executive Editor
LLEW KELTNER, M.D., Ph.D., Roundtable Moderator

We are all partners. Life is partnership — life and death. As individuals cast at birth into a vast net, we habitually ignore this web of connections as mere background, but it is always there, whether we cooperate or struggle against it. Like greatness, some people and the organizations they build seek alliances as the very stuff of life. Others have partnering thrust upon them.

With the new rise of cancer immunotherapy, the use of combinations is an emerging paradigm that demands a new kind of collaboration among all the key players, from key opinion leaders to companies to regulators to payers. What looks like competition between immuno-oncology mechanisms and therapies is that and more. Everyone wants a place in the ideal combination, but to get there, each one must collaborate with the others, if only in conversation and debate.

Our series of virtual roundtable discussions on combination cancer immunotherapy enters a new phase with this installment. Part Three moves from the KOLs in the first two parts to the leaders of companies developing advanced cancer immunotherapies and all vying for a place in the coming combinations. One of our goals was to compare the views of KOLs and companies by enlisting both groups in the roundtable panel and posing essentially the same set of questions to everyone.

PART THREE: COMPANIES AT STAKE

In this part and continuing in Part Four next month, we will hear from the leaders of many key companies in the field. Their stake in the race — or is it partnership? — consists of capital, real assets, and other forms of value, including people, knowledge, and a genuine desire to change the ugly visage of cancer. In many ways, each one's fate depends on what it does not only to compete against but also to cooperate with the other contenders.

We have changed the roundtable format here, from the question-by-question KOL discussion in Parts One and Two, to a company-by-company presentation — a necessity, given the high number of responding companies. We did our best to invite and include all of the companies now developing cancer immunotherapies, chiefly in the new areas generating the most excitement in the oncology community: checkpoint inhibitors, co-stimulators, and complementary immunostimulators such as cancer vaccines and ablative modalities that promote immune-cell production. We also hear from a few companies that believe other approaches deserve a place among the possible cancer immunotherapy combinations the roundtable addresses.

The questions we asked the panelists were as follows:

Why combinations?
Do you believe cancer immunotherapies should be used in combinations rather than as single agents, or is it possible to envision a single effective immunotherapeutic agent?

Essential components?
In your opinion, if cancer immunotherapy combinations are essential, what are the essential constituents of any combination therapy?

Backbone therapy?
Will a particular approach such as PD-1/PD-L1 be the "backbone" of cancer immunotherapy combinations? Or will consensus on a hierarchy of therapies continue to evolve with the growth of scientific understanding in ongoing research?

Combo criteria?
By what criteria will physicians select specific immunotherapy combinations for individual patients or patient groups? Or will regulatory and reimbursement realities dictate the combinations?

Narrow or wide applications?
Will the most effective immunotherapy combinations be specific to traditional cancer indications (NSCLC, HCC, etc.) or tend to have general effectiveness against all or a wide range of cancers?

Personal or broad?
Do you see limits on the practice model for cancer immunotherapies; i.e., will cell-based approaches remain restricted to a small number of patients in intensive-care or salvage settings?

Commercialization challenges?
What are some of the major hurdles you face in commercializing your cancer immunotherapy product or products, especially considering the science, regulatory pathway, and market are still evolving?

General comment?
Is there anything else that you believe is critical to understanding how combination immunotherapy or another immunotherapeutic approach will move into use as the backbone of cancer therapy?

The following are the responses:

GLAXOSMITHKLINE

In early development of numerous cancer immunotherapy candidates with a variety of mechanisms.

AXEL HOOS, M.D., PH.D.
Vice President, Oncology R&D

Why combinations?
Some immunotherapies have proven effective as single agents. They have not yet been maximized in their benefit for patients. Combinations may maximize benefit and potentially enable cure.

Essential components?
Aim for synergistic pathways. Three main categories: 1) checkpoint modulators with each other to minimize immune suppression; 2) checkpoint modulators with other immunotherapies to reduce immune suppression and specifically activate immune responses; 3) immunotherapies with targeted therapies to leverage immune effects and targeted therapy effects (e.g., speed of effect, debulking, immune modulation, etc.).

Backbone therapy?
In the short term PD-1/PDL-1 and other checkpoint modulators, as they become available, will be the backbone of immunotherapy combinations based on their clinical efficacy and safety profile and their universal utility. With further evolution of other immunotherapy modalities, this may shift slowly based on the demonstrated effects.

Combo criteria?
If approved and reimbursed, immunotherapies will be selected for combinations based on their clinical benefit/risk profile in the respective population. Research addresses rational combination possibilities based on mechanistic synergies and characterization of immune effects of non-immunotherapy combination candidates.

Narrow or wide applications?
A wide range of benefits is possible depending on the combination; e.g., for targeted therapy/immunotherapy combinations, most limitations are imposed by the targeted therapy. However, current development practices dictate development in histology-defined indications. With demonstration of wide benefit across boundaries of histology, it may be possible to modify these standards over time.

Personal or broad?
Immunotherapies should be as broadly

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accessible to patients as possible. However, limitations will be imposed by practicalities such as antigen expression, scalability of the approach, effect size, alternative options, etc. For cell-based approaches limitations may be greater than for more generic approaches.

Commercialization challenges?

Assuming we generate the needed clinical data on benefit/risk for any given immunotherapy or combination, the main challenges will be pricing and patient access. Particularly for combinations, the current pricing model will lead to very high costs for reimbursement agencies and may be prohibitive in some geographies. Building a new pricing model for combinations should improve this situation. For example, one could envision pricing a novel-novel combination as a regimen and not as individual drugs, thus introducing substantial discounts relative to individual pricing. The industry would benefit from working together to introduce new pricing models.

General comment?

Collaboration is going to be paramount to maximize value and speed to make combinations with immunotherapies a reality. Trends toward that are visible across the industry. Further, the evolution of an immunotherapy-focused clinical development and regulatory paradigm, which was started by the Cancer Immunotherapy Consortium (CIC) about a decade ago, will further increase the probability of success for new therapies.

BAVARIAN NORDIC

Developing targeted cancer immunotherapies and vaccines; lead candidate is a viral-vector antigen-targeting therapeutic for prostate cancer in Phase 3.

JAMES BREITMEYER
Division President, Cancer Immunotherapy, Bavarian Nordic Inc, and Executive Vice President, Bavarian Nordic A/S

Why combinations?

Although a single effective immunotherapeutic agent no doubt exists, there is also great promise for taking existing and future agents into combinations. A single agent would have to have three essential actions: targeting the immune system toward the tumor, potently stimulating a positive immune response, and overcoming the natural resistance to the immune system many tumors express in their microenvironment. We are testing our poxvirus-based cancer immunotherapies alone and with a variety of immune checkpoint inhibitors, and are generating some very exciting single agent and combination data, both in animal models and clinical trials.

Backbone therapy?

The very impressive efficacy results coming in with PD-1/PDL-1 antibody blockade suggest that immune checkpoint inhibition may be central to cancer immunotherapy. However, one potential disadvantage to using immune checkpoint inhibition alone is its autoimmune side effects, reported to involve variably skin, lungs, the gastrointestinal system, and the endocrine organs. Further, some patients respond fabulously, but others do not. Patients who cannot mount an endogenous T cell immune response will not respond to checkpoint inhibition and must have their immune system specifically activated and directed toward their tumor. Active cancer immunotherapy using tumor antigens presented as proteins or as viral or DNA vectors may fill this gap. Such combination therapy may also address the nonspecific autoimmune effects of checkpoint inhibitors by focusing the patients' immune response on the tumor rather than on normal tissues.

Combo criteria?

In principle, each person's immune system has the potential to become educated to recognize the tumor and suppress its growth with productive immunity. The timing to achieve effective anticancer immunity may depend on the combination deployed. We will know better how to configure combinations as people become more educated about immunotherapy and the old treatment paradigms melt away. In the studies that won its approval, ipilimumab improved overall survival in melanoma patients without a significant effect on progression, something oncologists do not normally see. Many immunotherapies produce delayed responses, and sometimes patients even show shrinkage or response of their tumor at some point after the immunotherapy has been completed. We hypothesize that targeted activation of an antitumor immune response (foot on the gas pedal) coupled with blocking immune suppression (foot off the brakes) has the potential for synergistic clinical benefit in a broad population of cancer patients.

Personal or broad?

Active immunotherapies for cancer are generally very well-tolerated, with side effects more like vaccines than other traditional anti-cancer therapies such as chemotherapy or radiation. This suggests they may be broadly applicable and given at some point to many cancer patients. Some therapies, such as those that require the patient's cells to be harvested and processed outside the body, may have more limited applications.

Commercialization challenges?

Targeted therapies and immunotherapies will likely be pricey at first because they are complicated to develop in the laboratory and require a full-blown clinical development program. Immunotherapies will initially be used in a focused way; not everyone will get immunotherapy in the early days, at least. Payers will worry about combinations of expensive treatments, and they have few precedents for how to keep their overall system costs in control. There will be scrutiny and demands for good, solid clinical data to support reimbursement decisions.

There is skepticism about the viability of some kinds of immunotherapy in general, and particularly in the investor world. Anti-PD-1/PD-L1 success has become a lightning rod, and it seems

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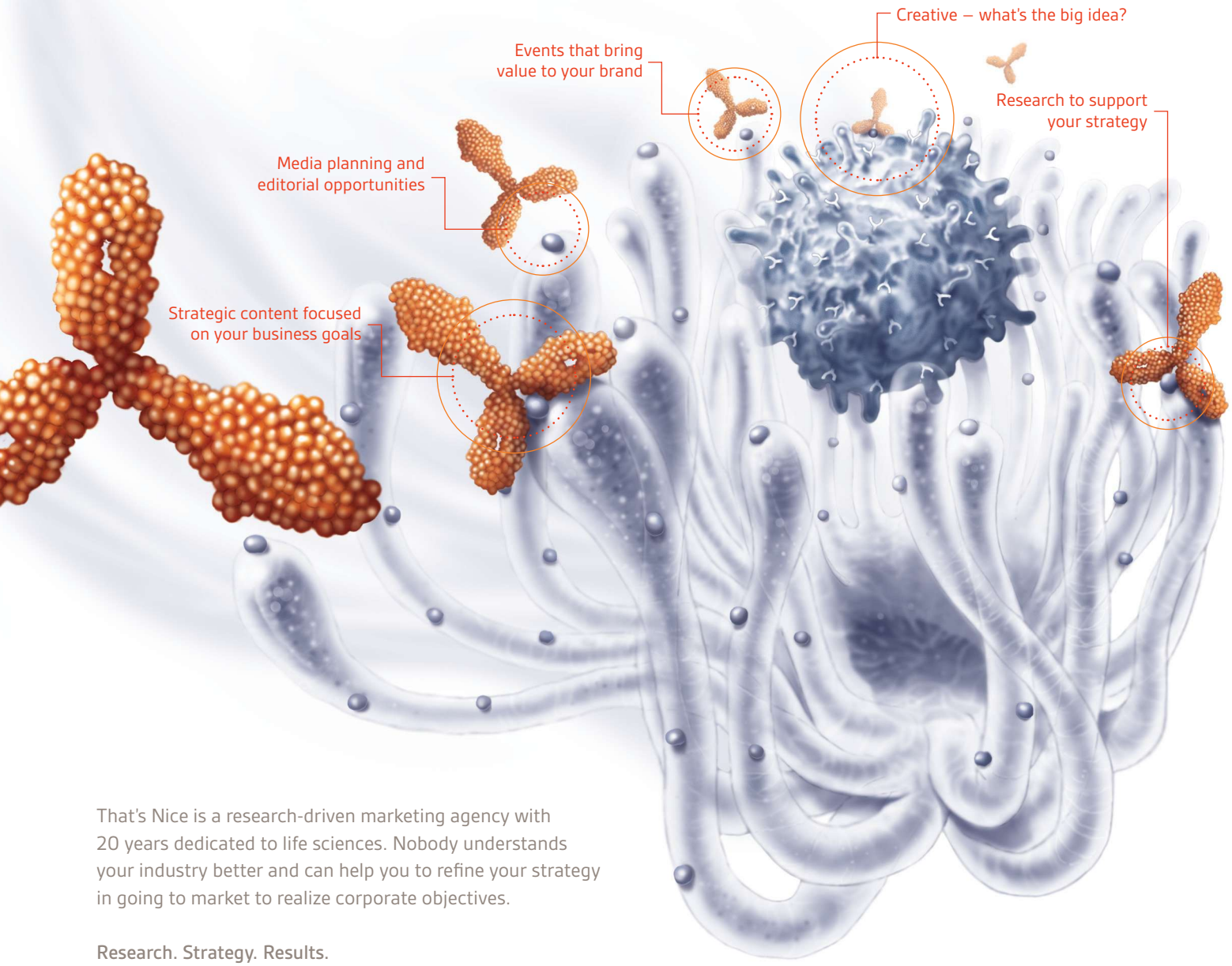

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everyone is scrambling to buy the next checkpoint antibody, push it into the clinic faster, or try for breakthrough designation. But in other areas, such as active immunotherapy or cancer vaccines, there is still skepticism, particularly among investors and potential commercial partners. Another hurdle is that some physicians and investigators understand how immunotherapy may be different from chemotherapy, hormone therapy, or radiation; others do not. The knowledge base around immuno-oncology for cancer therapy is expanding exponentially as more clinicians treat patients with this novel treatment paradigm.

TAKEDA/MILLENNIUM

Exploring development of next-generation immunotherapies.

MANFRED LEHNERT, M.D.
VP and Head, Innovation Oncology Therapeutic Area Unit, Takeda Pharmaceuticals

Why combinations?

The major benefit of single agents has been limited to a subset of 20-40 percent of patients in certain diseases. There is a strong mechanistic rationale for combinations, and there is preclinical and early clinical data to support that.

Essential components?

At this point, anti-PD-1 or anti-PD-L1 would seem the backbone of clinical combination development. But this may well change in the future, when we better understand the clinical activity and safety profile of the many other agents and approaches that are in development. It may well be that optimal immune-therapy combination will depend on disease context (disease type and/or stage), and may be guided by molecular information from tissue (tumor and/or adjacent normal) and/or blood.

Combo criteria?

This will be largely driven by a mechanistic and scientific rationale and differential clinical benefits. It would seem inconceivable that oncologists may consider combining individual immune-therapeutics in routine clinical practice without robust benefit-risk evidence from well conducted clinical trials.

Personal or broad?

It seems likely that these two general approaches are not mutually exclusive, and each will play an important role in the same or different diseases.

General comment?

The field of therapeutic cancer vaccines has remained largely unsuccessful to date. But this may change through improved vaccine technology, personalization of vaccine therapy, and perhaps most importantly, concomitant or sequential combination with therapies that break immune tolerance.

IMMUNOVACCINE

Early clinical-stage development of DepoVax vaccine adjuvanting platform and product candidates for cancer therapy.

MARC MANSOUR, PH.D.
Chief Executive Officer

Note: The company's science advisor, Neil Berinstein, M.D., Director of Translational Research at the Ontario Institute for Cancer Research (OICR), and Marianne Stanford, Ph.D., Director of Research, contributed to Dr Mansour's response. Dr. Berinstein also participated in the KOL discussions in Parts One and Two of this series.

Essential combination components?

We need at least two components to "drive" effective cancer immunotherapies: We need a therapy, such as an effective cancer vaccine, to "push the accelerator," or facilitate anti-tumor immune responses, and a component to "release the brakes," or limit the immune suppressive forces that impair generation or effectiveness of the anti-tumor responses. Thus, we need to generate or provide effective tumor-specific T cells and also provide active but safe immunomodulators such as checkpoint inhibitors.

Combo criteria?

Ideally, specific immunotherapy combinations will eventually be selected based upon the patient's tumor-expression profile and immune status. Initially, we will likely select treatments based upon data from trials that demonstrate the effectiveness of certain immune therapies and combinations in specific tumor cancer types and tumor stages. The biologic differences between tumor types and stages of tumor progression will prevent extrapolation into additional clinical indications without the relevant trials. Regulatory authorities will likely take this perspective until proven otherwise.

Personal or broad?

There are many types of personalized medicine used in clinical practice today, including surgery and autologous or allogeneic transplantation. Thus, it is likely that effective cell therapy or other immune therapies will be made available clinically. The more significant concern is how to reduce toxicities, particularly in early, high-risk clinical situations where risk of recurrence is high but the patient only presents microscopic disease. We need well-tolerated therapies, and off-the-shelf combination therapies will likely be more applicable than cell-based therapies such as CAR.

Commercialization challenges?

The evolving science in cancer immunotherapy has a significant impact on clinical trial design, particularly in the areas of analysis of clinical responses and the appropriate selection of patients to enroll in trials. We must identify the optimal immune modulators and immune-modulator combinations for the clinical indication being addressed. The issue of clinical responses to immunotherapy has been partially addressed through the irRC, or immune related RECIST criteria, but the uptake of irRC in pivotal trials has been slow. Preliminary

data has also indicated that biomarkers and genetic signatures may be used to identify the patient population that will best respond to treatment, but validation of the biomarkers for selection has yet to be confirmed in the clinic.

General comment?

We highly value our preclinical data as a driver for clinical programs. We believe that well-conducted studies may help with the rational design of combination therapies and can assist in the appropriate design of clinical trials. Having said that, demonstrating a mechanism of action for the therapy in patients early on is critical to justify further development. This will allow for more efficient, effective, and innovative clinical trial designs that will translate into effective cancer therapies.

MEDIMMUNE/ASTRAZENECA

Numerous immunotherapies in development, including MEDI4736 (PD-L1) now in Phase 3, tremelimumab (CTLA-4, licensed from Pfizer), MEDI6469 (OX40, from AgonOx), and MEDI0680 (PD-1, acquired through Amplimmune).

BAHIJA JALLAL, PH.D.
Executive Vice President, AstraZeneca, Head of MedImmune

EDWARD BRADLEY, M.D.
Senior Vice President, R&D Oncology, iMED Head

REG SEETO, M.D.
Vice President, Head of Partnering and Strategy

Why combinations?

[BRADLEY] We believe in combinations and have a robust clinical portfolio with CTLA-4, PD-1, PD-L1, and OX40 in development both as monotherapy and in combinations. The next wave of combinations for us is not just immunostimulators and checkpoint inhibitors, not just the gas on and brakes off. We are looking at the tumor microenvironment and promoting the enhancement of tumor antigen presentation, so we are focused not only on the adaptive immune system but also the innate system.

Essential components?

[SEETO] Everything is driven by the science, and we need to conduct more

> "The evolving science in cancer immunotherapy has a significant impact on clinical trial design."

MARK MANSOUR, PH.D.
Chief Executive Officer

experiments to understand the essential combination components. Dr. Yong-Jun Liu, our new head of research, is a world leader in the field of immuno-oncology, so in addition to our focus on combinations, he has brought a whole new way of thinking about how we approach combination therapy.

Backbone therapy?

[BRADLEY] Obviously, the cornerstone of our immunotherapy strategy is combinations, and in those combinations there will be certain backbone approaches, but the optimal combinations are still being determined, and that is why there is so much activity at the moment to identify them. Still, although there is a great deal of talk about the second wave of immunotherapy, the therapies that are in the lead today will likely be the backbone therapies for optimal combinations for a long time.

Commercialization challenges?

[JALLAL] There are no significant differences in the challenges for immunotherapies and other types of cancer drugs. We deal with several stakeholders. The first one is the patient — we must make sure whatever we do is backed up with data. If we say our drug should be used in a combination, the use must bring more benefit to patients. The second stakeholder is regulatory authorities, such as the FDA. We must deliver data that supports putting the combination use on our label. The third stakeholder is the payer, to whom we must also show data that differentiates our treatment in combination, plus cost-effectiveness data. We are right on track with our stakeholders in all respects right now.

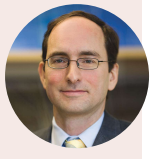
Obviously, there are more complications if the combination includes not only our drugs but also ones from other companies. However, we have a broad portfolio, and most of the combinations we are developing now consist of molecules we have in house, and that gives us more flexibility and control over how we can price the combinations. We don't develop drugs just for the sake of developing them — we want patients to have access to them. You have to work with all the stakeholders to make sure as many patients as possible can gain access to your drug.

[BRADLEY] Another consideration: Immune-mediated therapies take time to generate the immune cells that travel to tumor sites and kill cancer cells. Sometimes the biological effects take weeks to months. Physicians must realize there is a different pace of response, and the tumor may even seem to get a little larger at first, due to an inflammatory response, but it will then shrink and sometimes go away. What is surprising is how quickly physicians have, in fact, learned to deal with some of the differences in side effects.

JUNO THERAPEUTICS

Developing novel immunotherapy platforms that harness the potency of memory T cells, redirecting them to targets expressed on or in cancer cells; three candidates in Phase 1 – 2.

MARK W. FROHLICH, M.D.
Executive Vice-President, Research & Development



Why combinations?

Historically, combination therapy with traditional agents has been the cornerstone of oncology. With novel immunotherapeutics, and an increased understanding of mechanism of action, there has never been a stronger rationale for combining drugs. In the short term, we need to combine drugs with potentially synergistic mechanisms. In the longer term, we can potentially combine multiple therapeutic avenues within our engineered T cells by modulating pathways within the T cells or using them as a vehicle to deliver molecules to the tumor microenvironment. For example, cytokines that would be toxic when delivered systemically could be delivered to the tumor by the T cells to provide potentially synergistic, or at least additive, antitumor effects.

Essential components?

Engineered T cell therapy and checkpoint blockade are two of the most exciting approaches. Checkpoint inhibitors are already approved for certain indications; they don't appear to be working in all tumor types or patients but will be an important building block with which we can start mixing and matching in rational combinations. Used together, taking the brakes off and pushing the accelerator —providing cells specifically activated to target the cancer — will be important to test, particularly in the challenging solid tumor setting.

Backbone therapy?

Engineered T cells and checkpoints inhibitors can potentially serve as therapeutic backbones. However, earlier in the treatment paradigm, as in the adjuvant setting where only microscopic amounts of tumor remain, there may be insufficient antigen to stimulate a T cell response to a checkpoint inhibitor or to stimulate the proliferation of engineered antigen-specific T cells. In those settings, a vaccine to simulate T cell proliferation may be important as one of the therapeutic backbones in combination with the others.

Combo criteria?

Biologic rationale based on the mechanisms of action will be used to prioritize testing of combinations. Preclinical models may provide additional insights, but ultimately, combinations will need to be tested empirically in the clinic.

Narrow or wide applications?

Initial approvals will be in advanced patients with relatively narrow indications based on single arm trials in some cases. Subsequent confirmatory trials earlier in the treatment paradigm will be randomized and address larger patient populations. If dramatic anti-tumor effects with clear clinical benefit are observed in individual patients, then we can anticipate that cohorts of patients in smaller indications could be sufficient for label expansion or at least reimbursement.

Personal or broad?

Initially, combinations will be tested on groups of patients rather than on individuals. By appropriately investing in biomarkers that can help predict which patients are benefiting, we will have the opportunity to tailor the agent or combination to a particular patient. Some of the pathways or immune mechanisms are common across various disease types, and it is possible to imagine moving towards a paradigm where we screen patients for a biomarker and treat them based on the biomarker, as opposed to whether they have a particular cancer type.

Commercialization challenges?

Historically, companies have been hesitant to let their drugs be tested in combinations prior to obtaining regulatory approval. That appears to be changing, and we are seeing several companies partner on combination studies early in the drug development process. Regulators also are more receptive to new approaches to bringing combinations to market. Cost of goods will need to be controlled with novel biologic therapies, but the increased clinical benefit that can potentially be provided by these approaches should still translate to value for patients and payers.

We have run as many company responses as space allows this month and will follow with the remainder next month and beyond if needed to follow this rich vein of lessons in translational R&D, business development, scale-up, and commercialization of breakthrough medicines. We are still open to hearing from other companies that either missed our first invitation or believe they belong in the conversation. Meanwhile, please join the discussion on Twitter at #CCIRLSL.

Cannabis-Based Pharmaceuticals: The Next Frontier?

CLIFF MINTZ Contributing Editor

The current U.S. legal/regulatory landscape has given rise to two distinct types of companies that are attempting to commercialize cannabis products. The first of these is commonly referred to as medical marijuana companies, or as Steven Schultz, VP of investor relations at GW Pharma suggested, "nutraceutical or herbal remedy companies that promote the medicinal properties of cannabis."

Typically, products from these companies are botanical extracts or actual plant materials derived from specific cannabis strains with anecdotally-reported medicinal properties that can be topically applied, ingested, smoked, or vaporized. Patients require a prescription from a licensed physician to obtain medical marijuana, and it can be used only in states that permit consumption of cannabis for medical purposes. Interstate transport of medical marijuana (even between states with medical cannabis legislation in place) is prohibited by federal law.

Unlike medical marijuana companies, biopharmaceutical companies, including GW Pharma, Kannalife Sciences, Aphios, and others, are committed to developing cannabis-derived pharmaceuticals using conventional U.S. FDA regulatory approval pathways. "The idea behind our approach is to offer the market, and more importantly patients, a medicine that has been through a full regulatory review and is well characterized regarding efficacy, safety, and interactions with other drugs," offered GW Pharma's Schultz. He added, "None of those things are present in medical marijuana offerings."

Likewise, Dean Petkanas, CEO of New York-based Kannalife Sciences, a phytomedical company that is developing cannabis-based drugs to treat hepatic encephalopathy and other neurological disorders, said, "Doctors want to know what they are prescribing to their patients and anecdotal evidence about the therapeutic benefits of a plant-based nutraceutical grown by 'new-age-pot-farmer-wanna-be-pharmacists' is simply not going to cut it. Also, added Petkanas, "In the case of some intractable diseases, there will be a need for extremely potent pharmaceutical cannabis-based products, which normally cannot be achieved using even the best plant-based extraction technologies."

While the business case for developing pharmaceutical cannabis-based drugs is sound, the cost and time required for regulatory approval of these products will be much greater than those required for commercializing medical marijuana products. Put simply, medical marijuana products will be commercialized first and likely garner an early majority share of the rapidly emerging medical cannabis market. "Not to worry," offered Trevor Castor, CEO of Boston-based Aphios Corp., a biopharmaceutical company developing cannabinoid-based products to treat emesis (nausea and vomiting), cachexia (wasting diseases), and CNS disorders like MS and Alzheimer's disease, "the market is large enough to support both the nutraceutical/herbal remedies and pharmaceutical sides of the business. They can easily coexist in today's marketplace." Further, by way of an example, Castor pointed out that the multibillion-dollar omega 3 fatty acids market comfortably supports the sale of both dietary supplements and FDA-approved, prescription-only omega 3-based pharmaceutical products.

Unlike most companies in the cannabis-based pharmaceutical space (mainly focused on developing cannabinoids as therapeutics), Potbotics is a biotechnology company that has combined robotics and artificial intelligence to ostensibly streamline cannabis pharmaceutical development. The company is commercializing a product called Brainbot, a physician-facing tool designed to identify the right combina-

tion of cannabinoids found in specific marijuana strains to maximize the therapeutic benefits of cannabis for treating patients with concussions, epilepsy, and other neurological indications. "Think of Brainbot as a super EEG medical device that allows healthcare providers to evaluate and quantify in real time a brain's reaction to specific strains of marijuana," explained David Goldstein, Potbotics CEO. Goldstein added, "This will allow healthcare providers to analyze and determine the right ratio of cannabinoids [and make strain recommendations to patients] for optimal treatment of certain neurological indications."

CLINICAL TRIAL CHALLENGES

Cannabis's classification as a Schedule I drug (i.e., illegal with no current medical value) makes medical cannabis research extremely difficult. Also, while the FDA has signaled a willingness to review new drug applications for cannabis-based therapeutics, the agency has yet to issue definitive guidance for regulatory approval of these products.

"The confusion between federal and state laws is a major factor that is causing hesitancy among regulatory bodies regarding the approval of cannabis-based products," said Castor. For example, he offered, "Federally, a drug cannot be prescribed unless it has undergone clinical trials, yet many states have passed legislation allowing the use of medical marijuana without clinical trials and without identifying specific indications. This must be resolved to ensure patient safety." Likewise, Petkanas believes that cannabis's designation as a Schedule I drug is a serious impediment and one that will need to be resolved to commercialize

"In the case of some intractable diseases, there will be a need for extremely potent pharmaceutical cannabis-based products."

DEAN PETKANAS
CEO of Kannalife Sciences

"The market is large enough to support both the nutraceutical/herbal remedies and pharmaceutical sides of the business."

TREVOR CASTOR
CEO of Aphios Corp.

cannabis-based products. He said, "The legal patchwork for cannabis that has evolved in the U.S. suggests that cannabis-based therapeutics will be available only in certain states (which will restrict patient access) and also make it very costly for companies to underwrite product launches in individual states."

Unlike other prescription drugs, which are exclusively in the purview of the FDA, cannabis-based therapeutics require input from the U.S. Drug Enforcement Agency (DEA). And, the current political mindset at the DEA is not favorable for the current and future development of cannabis-based products. "THC is the only cannabinoid that has any real psychotropic effects, and, despite the possible therapeutic benefits of other cannabinoids like CBD and CBG, they are Schedule I substances, which makes developing any cannabis-based pharmaceuticals quite challenging," lamented Castor. Petkanas was more sanguine about cannabis's designation as a Schedule I substance. He said, "The Controlled Substance Act needs to be repealed, changed, or simply allowed to wither away to ensure that much needed cannabis-based drugs can be brought to market to address unmet medical needs."

TECHNICAL/MANUFACTURING CHALLENGES

There are also several technical and manufacturing issues that must be addressed before cannabis-based pharmaceuticals can be successfully commercialized. First, substantial investment must be made in production facilities to breed and grow various cannabis strains to obtain appropriate chemical compositions to treat specific therapeutic indications. According to Petkanas, this investment must include research on breeding programs, strain construction, cannabinoid concentrations at different stages of plant growth/harvest times, and yield improvements. "As strange as this may sound, crop failure [not having a redundancy of supply] is a serious issue that all players in the medical cannabis industry must address," mentioned Petkanas.

Second, plant growth, extraction processes, and manufacturing active cannabis-based therapeutics must be conducted according to current good manufacturing practices (cGMP) and rigorous quality standards. "The whole point of seeking regulatory approval is to demonstrate to patients and healthcare providers that our products have been thoroughly reviewed are well characterized and determined to be safe and effective," stressed GW Pharma's Schultz.

Third, the method and route of delivery of cannabis-based pharmaceuticals for individual indications will be vitally important. While smoking cannabis is currently the most obvious method to deliver desired therapeutic effects, it may not be the most effective way to maximize its medicinal benefits. "Every patient is different, and we need to offer them alternate delivery methods to best treat their illnesses," offered Petkanas. He added, "You cannot lock-in on a single delivery technology or form of administration for these products." Castor agrees. "We are currently studying various routes of administration and investigating the use of controlled-release technology to improve the oral and topical delivery of our products to expand the use of cannabis-based products to new indications."

Finally, determining the appropriate cannabis-dosing regimen for individual therapeutic indications will be critical. Petkanas offered, "Right now we have extremely limited scientific information regarding cannabis-dosing regimens for individual indications. We have to get this right to instill confidence in patients and physicians that our products work and are safe."

PROVIDER/INSURANCE EDUCATION IS IMPERATIVE

Both Petkanas and Castor agree that the existing confusion about the legality of cannabis-based products will likely have an effect on insurers and third party payers. "At this point, it is really unclear whether payers are going to place these drugs on formulary and reimburse patients who use them medicinally," stressed Petkanas. Further, Castor suggested that, like the omega 3 fish oil market, where there are both nutritional supplements and omega 3 fatty acid-based prescription drugs, consumers may have to pay out of pocket for medical marijuana, whereas insurers may cover the cost of FDA-approved cannabis-based therapeutics.

Despite any of these challenges, it is undeniable that there is burgeoning demand for medical marijuana and cannabis-based pharmaceuticals in the U.S. However, while the American public appears to be ready for medical cannabis use, it is currently unclear whether physicians will be inclined to write prescriptions for these products. To that point, patient and healthcare provider education was cited by each person interviewed for this article as the single most important factor for successful U.S. commercialization of cannabis-based therapeutics. "Let's face it, if physicians don't understand these drugs and are not convinced that these products are safe and effective, then they certainly are not going to write prescriptions for their patients," emphasized Petkanas. Both Castor and Petkanas believe that cannabis-based products may garner FDA approval as early as next year. L

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Am I Learning from the Failure of Others?

TONY BENDELL

All leaders know there's a lot to be said for the old adage, "Good judgment comes from experience, but experience comes from bad judgment." Conventional wisdom says it's not strictly true, of course. You don't have to have gotten something wrong for the world to deliver you — and your company — a crushing blow. It just takes overlooking the possibility, however slight, that something may happen that could impact your company.

What is worse is that we now live in a world of rare, hard-to-predict events of monumental consequences, such as the financial crisis. Such events are almost ignored by our conventional risk analyses, since these don't account for everything you cannot conceive of. When chaos happens these days, it's often a new type of chaos. And it's happening with increasing frequency, diversity, and impact.

So, what to do? Doing nothing is not an option. Shareholders and stakeholders rightly expect more, or at least hold leaders accountable when the unpredictable happens. Not everyone gets a second chance anymore. A reasonable start is to look at the failures of others, but that alone is far from enough.

Professor Tony Bendell is an MD and Lead Trainer at the Anti-Fragility Academy. His book *Building Anti-Fragile Organisations* was published in June 2014 by Gower. He can be contacted at: tony@theanti-fragilityacademy.co.uk

MAKING YOUR COMPANY ANTI-FRAGILE

What we need to do is make our companies "anti-fragile." No, this is not just a new word for robust; Nassim Taleb published a seminal book on the subject in November 2012.

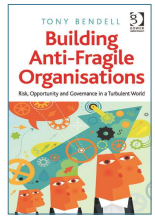
The difference between anti-fragile and robust is that the robust (e.g., company) is just waiting for a big enough wave to overpower it, since you can never be sure you are robust enough. In contrast, the anti-fragile gets stronger with every wave, stress, and shock. To a very large extent, I'm anti-fragile; I get stronger by exercising. So, how should you do the same for your company?

First, you probably need to do a fragility audit. Remember that, frequently, the more efficient your systems, the more fragile they are. Then, consider mechanisms for enhancing anti-fragility within your governance, strategy, people/culture, processes/operations, technology, supply chain, and other key dimensions of your organization.

Making each of these dimensions anti-fragile is potentially a real challenge, since you often need to borrow from existing good approaches while steering clear of a lot of bad management doctrine peddled by consultants and the business schools.

Anti-fragility is about learning, development, and growth — not about the corporation forgetting to think or suffering from bad governance, as so often happens in large organizations. The world is a dangerous place, and it's time to take stock. L

www.theanti-fragilityacademy.com



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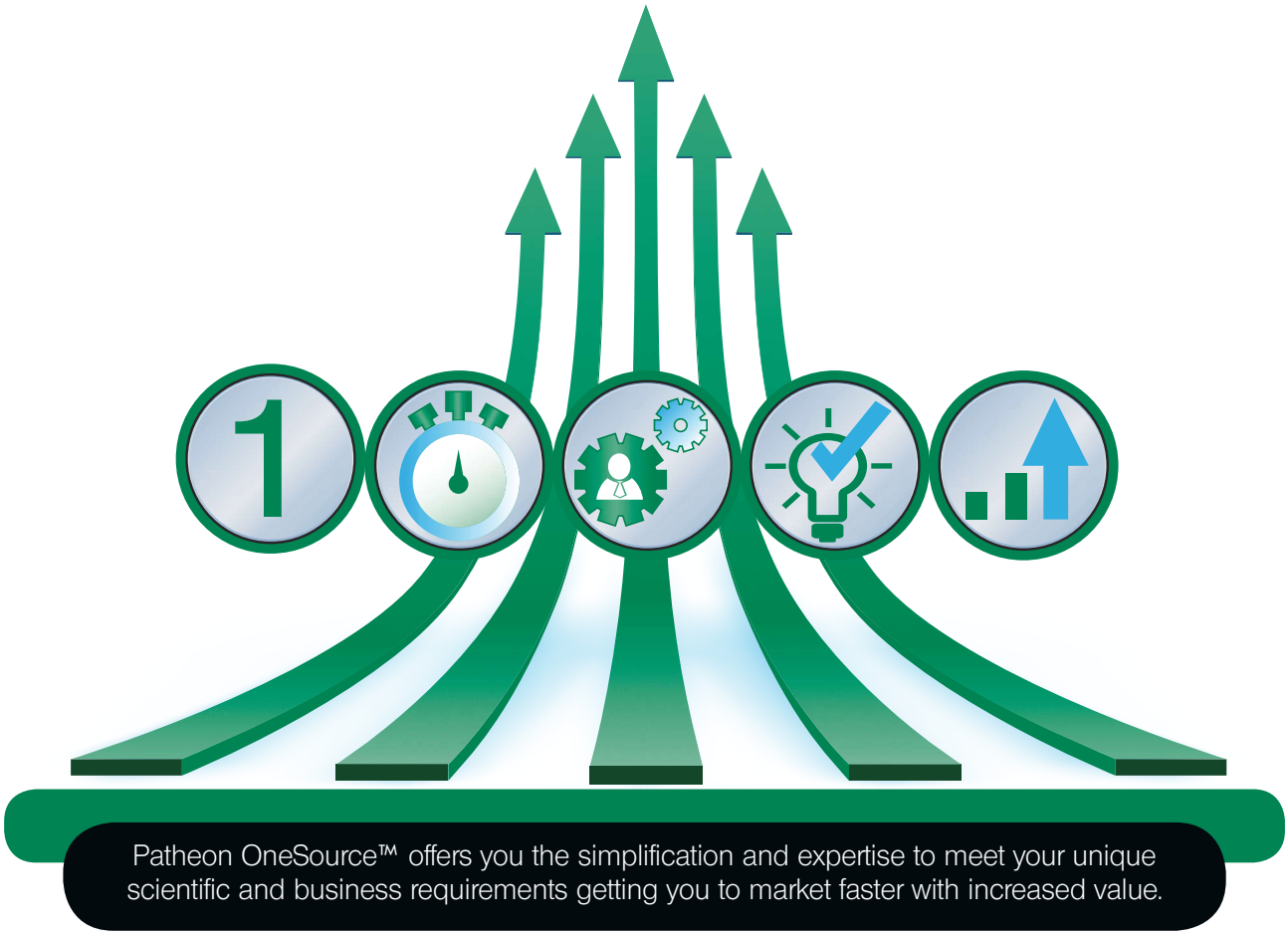

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