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Geno Germano
Group President of Pfizer's Global Innovative Pharma Business

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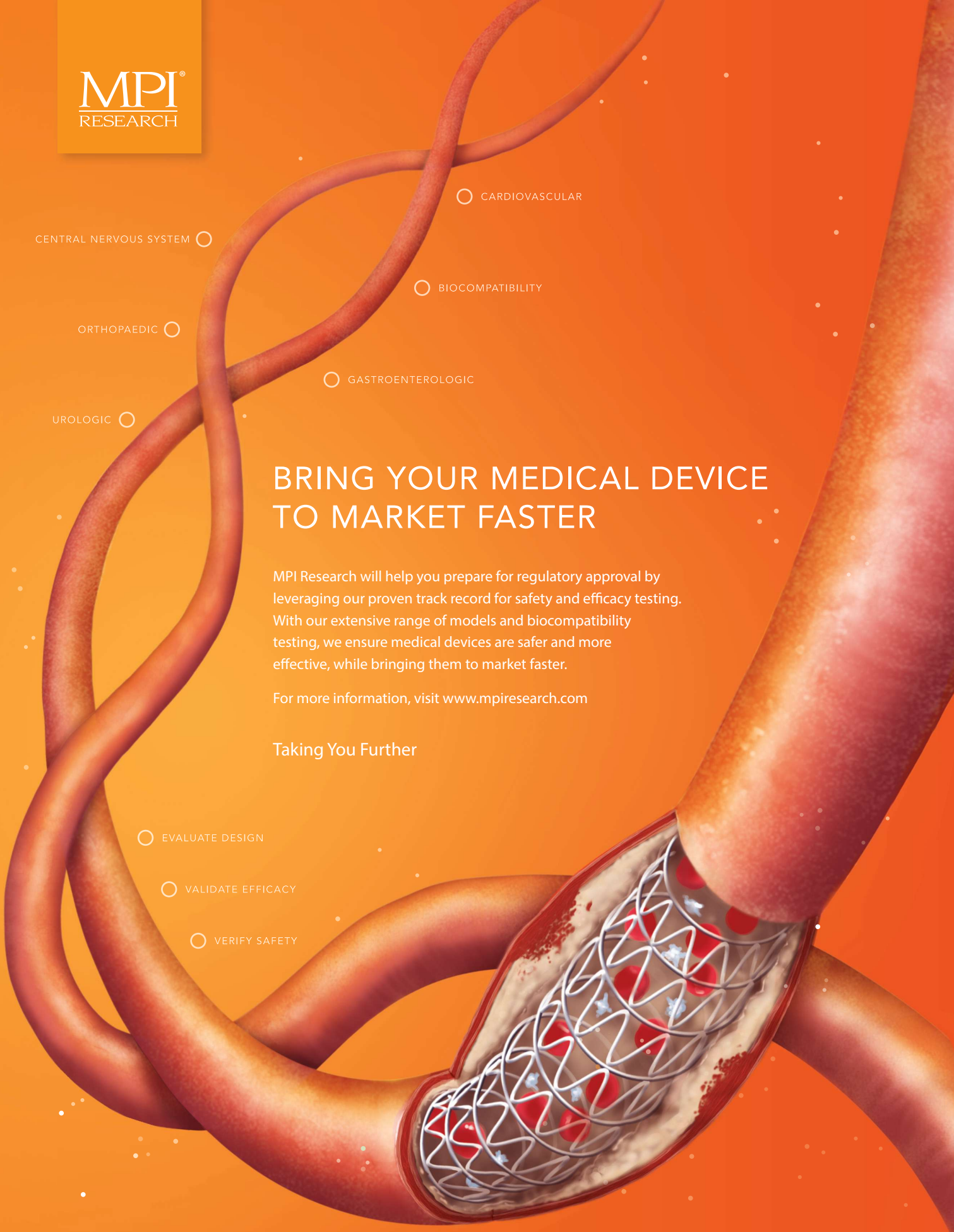

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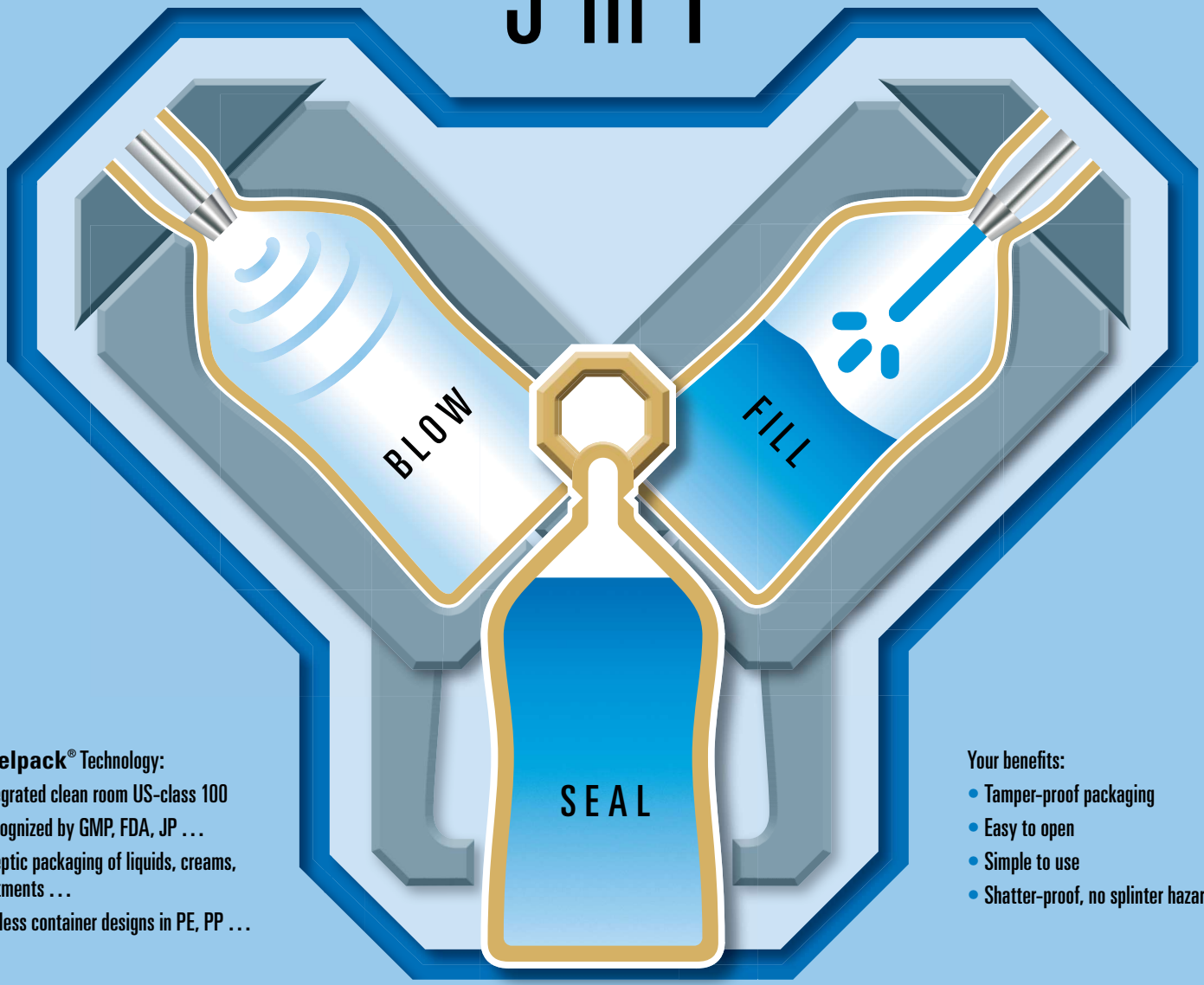

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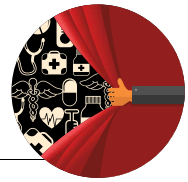

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What Is Required For Better Medical Research Participation?

ROB WRIGHT Chief Editor

Years ago I was asked to enroll my daughter in medical research. As I recall, the University of Buffalo physician approached me shortly before my child was to undergo a procedure. They were hoping to take a few additional tissue samples that wouldn't lengthen the procedure nor harm my daughter. I said no to this request. The clinician proceeded to provide some additional information (verbally), which came across as an effort to persuade me to reconsider. I declined again. He then said, "May I ask why you don't want to help advance medical research?" (Take a deep breath, Rob, as this doctor will be soon conducting a surgical procedure on your child). "Of course," I replied. However, I opted not to go into a lot of detail in my reply of, "I am simply not interested in signing my daughter up for research at this particular time."

Perhaps this last-minute approach by the doctor normally elicited a high acceptance rate. I imagine many parents are busy wringing their hands in worry, and probably don't put much thought into what seems like a rather simple and innocent request. Now to be sure, I was a little worried about my child. But having undergone the same rather routine procedure multiple times myself, I wasn't overly concerned. In fact, it was this experience which led my wife and I to mutually decide that only one of us should take off work to accompany our daughter on this day, and that one of us should be me. That's actually one reason why I said no to the last-minute research proposal; I didn't want to sign up my child without having the opportunity to discuss the decision with my spouse. Another reason why I said no was that my daughter was not in the room at the time of the request, but in the final phases of being prepped for surgery. While I doubt she would have fully understood the details of what was being asked, at least had she been present she would have felt included in the discussion and decision, instead of finding out after the fact that a choice had been made on her behalf. Sorry, despite my desire and willingness to help advance medical research, my wife and I are not interested in: (A) raising a person who isn't provided the opportunity to question authority and seek understanding; and (B) making unilateral decisions on behalf of our children without consulting each other, except in emergency situations.

We all know that the fuel of the biopharmaceutical R&D engine is clinical trials. If we want future cures and therapies for that which ails us, patients *need* the biopharmaceutical industry. Conversely, the biopharmaceutical industry needs people as willing and collaborative clinical trial participants, not mere subjects of study. In this month's issue you will find "A Behind-The-Scenes Look At The Patient Clinical Trial Experience" (see p. 50), which features the firsthand experiences of three research participants, including one parent who agreed to include her newborn child in a research study. We are thankful to all three for their willingness to transparently share their experiences, as well as for the people and organizations that helped us to connect. Though we continue to talk about our industry becoming patient-centric, especially when it comes to clinical trials, it seems we have a long way to go. Encouraging greater medical research participation isn't just what, when, where, why, and how you ask, but how you treat people throughout their disease journey. L

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Q What is the greatest insight gained from attending this year's BIO International conference?

A THE MOST IMPORTANT INSIGHT FOR ME was the shocking number of new faces and companies and the resulting number of new meetings this caused. Clearly the entrepreneurial spirit and state of innovation is alive and well when you look at all the conversations happening between new people with life-changing drug assets and new leaders with bold partnering mandates. Partnering assets with companies capable of completing late-stage development and commercialization of drugs with novel mechanisms (first-in-class targets) is my sole purpose for attending, and I had to work harder than ever to fit everything into my schedule.

ALEX CHANG, PH.D.
Director, Global Licensing & Business Development, Glenmark Pharmaceuticals, Inc., USA.

Q What is the greatest insight you gained from attending the Abuse Deterrence Formulation (ADF) Summit?

A TO OBTAIN ADF (ABUSE-DETERRENT FORMULATIONS) LABELING, companies must spend years and millions of dollars demonstrating bio-equivalence and efficacy of the new formulation. Yet without market exclusivity or favorable prescribing positions, the financial returns are insignificant. The conclusion reached at the summit is that abuse deterrence formulations may create barriers to the external manipulation of opioids; however, the motivated abuser will simply resort to ingesting multiple tablets to achieve the euphoric effects. This realization is forcing companies to rethink their abuse deterrence platforms and redirect development efforts to overdose protection when multiple pills are taken in an abbreviated period of time.

RON GUIDO
President of LifeCare Services and CEO of ExxPharma Therapeutics, a drug development and delivery company dedicated to formulating drugs to reduce abuse and overdosing.

Q What is the greatest insight gained from attending a recent conference and how do you intend to use it in your current role?

A AT THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) annual meeting, guest speaker Dr. Michael Porter, a Harvard economist, spoke on creating a value-based healthcare system. I was left thinking that the core challenge is really twofold: (1) how well we sort, analyze, and translate data into knowledge, and (2) our ability to work collectively ensuring diversity of input. The ability to respond to complex challenges creatively, whether one is designing a new drug delivery, building the factory-of-the-future, or creating a valued-based healthcare system, will require both competencies.

SANDRA POOLE, P.ENG, M.A.SC. CHE
Executive VP, technical operations at ImmunoGen

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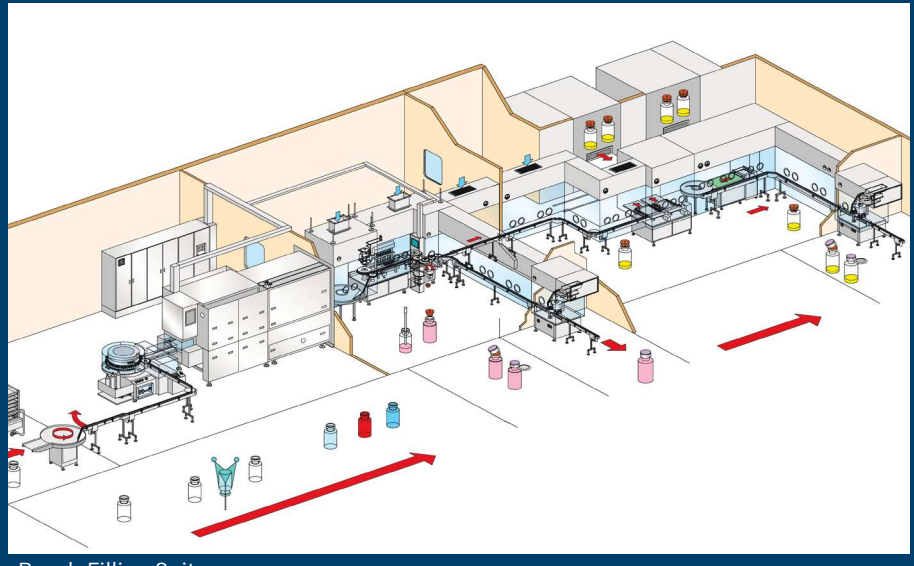

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Corbus Pharmaceuticals

Flipping the off switch in rare, chronic inflammatory diseases.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Corbus has the CB2-agonist Resunab (ajulemic acid) in development for three rare, chronic inflammatory indications: cystic fibrosis, systemic sclerosis, and dermatomyositis. The small-molecule compound is a "repurposed pharmaceutical." The drug triggers the mechanism or pathway by which inflammation returns to homeostasis (resolution of inflammation), allowing damaged tissue to heal. Phase 2 trials have begun in all three indications.

WHAT'S AT STAKE

A flare, a flame, a fan of fire spreading over fields and forest — a fitting image for inflammation, the inevitable and most often indispensible condition of having an immune system. Inflammation burns through hostile microbial invaders, damaged cells, and substances, but at times, unfortunately, healthy tissue as well, sometimes setting the stage for subsequent disease processes to unfold. Among the most consequential of the possible morbidities are cystic fibrosis, systemic sclerosis (or "scleroderma"), and dermatomyositis. Corbus is staking its future on developing new agents to address those diseases through the mechanism underlying all of them — an inflammation "off switch" related to the CB2 receptor pathway.

"We are focused exclusively on rare orphan, serious, typically life-threatening inflammatory diseases, often associated with fibrosis," says CEO Yuval Cohen. "Morbidity is typically severe, even terminal, as in cystic fibrosis, or very life-threatening as in scleroderma and dermatomyositis. There are about 8,000 orphan diseases, and more than half of them involve inflammation. What they all share in common is an immune system that basically won't shut up. It is activated and unable to restore itself back to normal."

Usually, of course, the immune system turns on in response to something like a pathogen, destroys the intruder, then turns itself off. By simple logic, then, immunity has an on switch and an off switch. Each one is different from the other, however, and both consist of extremely complex pathways. Anti-inflammatory drugs generally try to "jam" the on side of inflammation, which offers no single target for resolving the condition. But the Corbus approach is to trigger the off side — a step-by-step process called resolution — thereby restoring homeostasis and healing in the affected tissue. The trigger is CB2, a white-blood cell receptor that, when inflammation is involved, turns the "off" process on. Lead candidate Resunab binds with CB2 to initiate resolution. The FDA has given orphan designation to the compound in scleroderma, and Cohen expects the drug to receive orphan and fast-track status potentially for all three indications ultimately.

Most of the Corbus management team members have extensive drug-development experience and many have a Big-Pharma background, such as board Chairman Alan Holmer, the former president of PhRMA itself. By no coincidence, Cohen notes the "undisputed leader" of the inflammation-resolution field, Professor Charlie Serhan of Harvard Medical School, is on the company's scientific advisory board.

The company plans to acquire more assets but is committed to targeting rare diseases only, according to Cohen. "We are building a conveyor belt. We will find new assets in pharma or biotech or academia, then modify them if necessary, direct their development, and thus build a clinical program in rare inflammatory diseases — which will give us the luxury of avoiding sale of the company and thus have a happy ending to the story." The ending may include the company marketing and selling its own products, he says.

By Cohen's estimate, Corbus might need only three to four dozen reps to cover the cystic fibrosis market or any of the others it will target in the U.S. Most states, he says, have only one or two major treatment centers for CF, scleroderma, or dermatomyositis. He does allow, however, that the CB2 mechanism could apply to diseases with much larger populations, on the scale of asthma or arthritis, possibly spelling the need for commercial partnerships in the company's future.

YUVAL COHEN
CEO

Vital Statistics

10
Employees

Headquarters
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Finances

Launch financing round:
$10.3M
in April 2014

Total from callable warrants (called July 2015):
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Lead institutional investor: Perceptive Life Science Advisors. Nasdaq debut April 2015

Research partnership funding

NIH grant for dermatomyositis Phase 2 clinical trial at U. Penn

Cystic Fibrosis Foundation $5M Developmental Award for Phase 2 clinical trial in CF

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New Focus On Abortion Could Result In Government Shutdown

JOHN McMANUS The McManus Group

August is a strange time in Washington, D.C. Tourists in pink t-shirts, "I Love DC" visors, fanny packs, and tube socks still mill around the National Mall. But the professional political class has departed for the beaches, mountains, and anywhere else they can find a respite from the bickering, conniving, and scheming that defines the city, and by extension, the country. The grand marble halls of Congress are ghostly quiet, and in the evening those who remain can enjoy the echo of cicadas as twilight turns to black.

That tranquility belies a brewing storm that may shut down the government in October. Like the last government shutdown, it is deeply rooted in healthcare policy.

Two years ago, Senator Ted Cruz (R-TX) and the anti-establishment wing of House Republicans championed a fruitless effort to defund Obamacare implementation through the appropriations process. But that attempt was blocked by the then-Democratically-controlled Senate and resulted in a 16-day government shutdown.

Republicans eventually blinked. They lacked the 60 votes in the Senate to pass the bill, let alone the 67 to override a certain presidential veto. More importantly, they soon realized that the botched launch of Obamacare was a far superior thing to highlight than closed national parks and administration rhetoric musing on the ability to honor sacred government obligations should the shutdown continue.

This year, a government shutdown may occur due to the release of six ghoulish, undercover videos by the Center for Medical Progress depicting top officials of Planned Parenthood cavalierly negotiating the price of harvested fetal baby organs. Republicans are intent on depriving Planned Parenthood of the nearly half-billion dollars of federal funds it enjoys in the budget and Democrats are equally committed to ensuring those funds continue to flow.

Like many Americans, I don't identify with strident voices on either side of the abortion spectrum. As the healthcare legislative assistant for a pro-choice Republican in the 1990s, it took me about two weeks to hand off the entire abortion issue to a young and eager legislative correspondent because I could not stomach meeting with advocates on either side of the issue.

Yet, I was struck and horrified by the videos of Planned Parenthood executives negotiating the price of intact fetal organs over salads and a glass of pinot noir. They described how an abortion procedure could be altered to ensure sound delivery of the brain, heart, and liver or even "intact fetal cadavers," as Melissa Farrell, director of research at Planned Parenthood Gulf Coast Texas, put it. These procedures would yield extra revenue for the Planned Parenthood clinic — and in the case of the Gulf Coast office about $120,000 a month.

Hundreds of thousands of Americans shared my horror and disgust as they watched video No. 5 showing Planned Parenthood staff lamenting that fetal baby parts were not readily available at that moment because they were thrown in a bin, and that, "We had a really long day, and they're all mixed up together in a bag."

Defenders of Planned Parenthood have attacked the purveyor of the videos for its agenda and "heavily edited videos," but often denied even viewing the videos. White House Press Secretary Josh Earnest claims he has not seen the videos so cannot comment. Really? It's only the most controversial domestic issue afoot and the press secretary can't take the time to view a YouTube video? That is not plausible.

Sensing a shifting tide on the issue, Hillary Clinton, an ardent supporter of Planned Parenthood, called the videos "disturbing." That is a politically safe statement.

CONGRESSIONAL ACTION

Just before adjourning for the August recess, the Senate voted on a motion to defund Planned Parenthood. With a vote of 53-46, the measure failed to garner the 60 votes needed to overcome a Democratic filibuster.

But the primary order of business in September is funding the government, and Congress has failed to enact *any* of the 12 appropriations bills to fund the various agencies. The House passed six, but none have yet been considered by the Senate. This means that Congress must pass an omnibus appropriations bill — funding the entire federal government — or more likely a "continuing resolution" funding the government under current policy and at current levels. This creates a tempting vehicle to remove $500 million in funds from the besmirched organization.

With Congress away, focus has turned to emerging Republican presidential candidates who have almost uniformly demanded a defunding of the organization through a showdown on funding the government.

Before Congress adjourned, a House bill to defund Planned Parenthood quickly garnered 164 cosponsors, and Speaker Boehner's spokeswoman said the House will "of course" vote on the measure.

It comes as no surprise that the White House has threatened to veto any bill defunding the organization. A bill is unlikely to get that far. With the excep-

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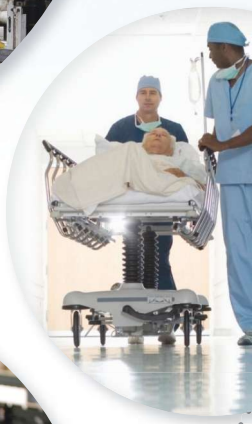

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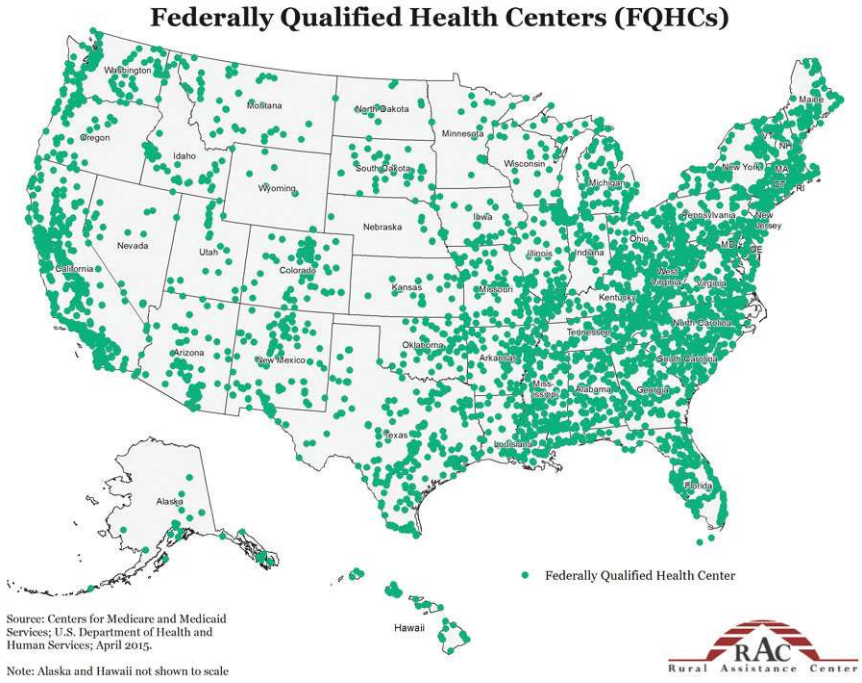

tion of Senators Manchin (D-WV) and Donnelly (D-IN) voting with Republicans, Democrats say they will continue to filibuster, arguing an attack on Planned Parenthood is an attack on women. Sen. Kirsten Gillibrand (D-NY) told The Blaze that although she has not seen the videos, "anyone who wants to defund Planned Parenthood wants to defund healthcare for women across the United States."

DEFUNDING PLANNED PARENTHOOD DEFUNDS WOMEN'S HEALTHCARE?

Defund women's healthcare? The "war on women" argument lacks merit and has received too much airtime. How does withholding taxpayer dollars from abortion clinics result in the end of cancer screenings and birth control? The Supreme Court's landmark Roe v. Wade ruling allows for abortion; it doesn't require taxpayers to subsidize the primary organization performing it.

Even if turning off Planned Parenthood's taxpayer spigot would result in the closure of every clinic, women can continue to receive free birth control and cancer screenings at any of the country's 9,000 community health center locations. Community health centers served 23 million people last year. They are ubiquitous and clearly accessible across the United States. (See above map.)

Planned Parenthood supporters also equate a vote to withhold federal funds with a vote against lifesaving medical research. To be sure, fetal tissue research has produced some significant discoveries, including vaccines and treatments for HIV, flu, hepatitis B and C, and eye diseases. The National Institutes of Health supports fetal research and spent $76 million on it in 2014.

But the value of legally obtained fetal tissue for medical research is not at issue. Defunding Planned Parenthood would not end fetal tissue research, just as it would not terminate birth control or cancer screenings.

The Democratic Leadership would disagree, and their insistence to prop open the doors of Planned Parenthood may not only prompt another government shutdown, but could very well set the stage for another Supreme Court battle with states alleging federal government coercion with Medicaid. In response to Alabama, Louisiana, and New Hampshire's recent actions to terminate Medicaid provider agreements with the maligned organization, the Obama Administration has warned that blocking funds may conflict with federal law.

The Centers for Medicare and Medicaid Services (CMS) reminded the states of 2011 guidance on the issue explaining that states may not exclude providers from Medicaid solely on the basis of the range of medical services they provide. CMS said states could exclude providers only under certain circumstances, such as when providers commit fraud or certain criminal acts.

So, what's next?

The fall is shaping up to include back-to-back standoffs with the Oct. 1 deadline to fund the government, and predictions that the U.S. will hit the debt limit just a few weeks later. The outcome of either process is anyone's guess right now, but the reawakened abortion debate could take center stage.

House and Senate leadership and the White House insist there will not be another government shutdown and we will not default on our debt. However, recent comments by all parties make it difficult to imagine a smooth path forward.

It is possible Congress narrowly avoids a shutdown. But, after the dust settles on yet another showdown, where will Washington find the bipartisan goodwill to push through the next round of debt-ceiling negotiations?

The cicadas stop chirping in late September.

Lindsay Bealor contributed to this article.

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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It's A Competitive Sport: Coming To Terms With Bio-Mania

ALLAN L. SHAW

"It was not too long ago that the surge valuations of multibillion-dollar biotech deals were negatively received by the capital markets."

In an environment where the pace of M&A and partnering deals has been nothing short of frenetic due to the industry's desire for growth, it is necessary to look externally for catalysts. The feeding frenzy we bear witness to is a manifestation of the competitive nature of this pursuit: Where "time is the enemy, and the opportunity is now," companies scour the landscape to identify opportunities that leverage core technologies/competencies to drive growth, create value for stakeholders, and create new treatment options for patients. Given this trend, is there an imperative for strategic M&A and collaborations to succeed? If so, how is growth sustained in an increasingly competitive environment filled with expensive crusades from those companies with acquisitive ambitions?

Before tackling these questions, consider the irony of how quickly market sentiment can change perception of strategic transactions. It was not too long ago that the surge valuations of multibillion-dollar biotech deals were negatively received by the capital markets. For example, several years ago Gilead's stock price tanked after the Pharmasset acquisition announcement. In contrast, Celgene's recent acquisition of Receptos was greeted enthusiastically with a soaring share price that reflected a rare NPV (net present value) positive deal. This shift in perception underscores the market's acceptance of the value-creating potential of such transactions; the fact that Gilead recovered the $11 billion price tag within one year of launching Solvadi/Harvoni has made this pill much easier to swallow.

The land grab phenomenon (discussed in detail in my article last month) has created a casino mentality in the capital markets, driving effective premiums to new heights (assuming the "real unaffected stock price can be determined" during bio-mania) while underestimating the considerations and work associated with mitigating the risks of picking the wrong horse. Put another way, this speculation is no different than the wagering that occurs in competitive sports, except in this case, every day is the Kentucky Derby, though with a lower probability of success. In a highly liquid environment with deals being consummated at a record pace and everybody being a target, it is easy to see how the industry has evolved into a spectator sport, being fueled by an-eat-or-be-eaten business-development mentality as investors cheer on companies.

The soaring valuations reflect the confluence of competitive dynamics: the insatiable demand for innovative assets relative to supply, investor expectations for the next big deal — and last but not least — a very liquid market. This dynamic leaves would-be purchasers no other choice than to pony up ever-larger checks and assume increased risk in order to gain access/exposure to exciting, innovative medicines/technologies. Consequently, the size of these bets is escalating in the face of eye-popping valuations, underpinned by scientific and regulatory risks with binary outcomes.

Given the increasing stakes, I thought it would be worthwhile to highlight some best practices that enable successful outcomes, whether you're in the hunt or deciding which jockeys to wager on. In my opinion, several fundamental ingredients to facilitate favorable outcomes are:

- crystal-clear focus on your needs/goals
- deep understanding of how to leverage your core expertise
- flexibility (e.g., structure, terms, consideration)

It is also important to remember that one size does not fit all, and there should be careful consideration of the alternative business-development strategies available in the toolbox to achieve desired goals. For instance, in some circumstances, buying a company outright is not always effective and

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efficient capital deployment. This is true particularly in acquisitions predicated by a lead asset whereby the acquirer is paying for assets they do not subscribe value to (e.g., rest of the target's portfolio). To better illustrate, when you want a steak, do you buy the cow? Collaborations, in contrast to M&A, offer many advantages over an outright acquisition (particularly with respect to precommercial assets). For example, collaborations combine the strengths of larger companies (e.g., global commercial reach and manufacturing capabilities) with the agility and entrepreneurial thinking of smaller companies. Such alliances play an important role in enabling capital/time-efficient development that complement and enhance core capabilities while allowing for developmental synergies. Of course, development-stage collaborations often serve as precursors to a merger — akin to dating before marriage. If pursued in a targeted manner, this strategy can provide significant pipeline leverage and diversification by cost-effectively increasing the number of shots on goal while diffusing risk (e.g., structuring deals that correlate payments to success-based milestones). Given the insatiable appetite for deals, the competitive environment is requiring much more flexibility on deal terms for would-be buyers desiring access to innovative technologies. The recent Celgene/Juno collaboration is a recent example of this emerging pay-to-play trend for access to groundbreaking experimental therapies, as evidenced by the deal's significant upfront cash and shift in risk.

The alternative approaches to business development are not mutually exclusive, and given the multitude of considerations and the need for flexibility and creativity, openness to a hybrid approach of innovative alliances, partnerships, and acquisitions may provide the most cost-effective framework. While there are no guarantees of success, executing a business development strategy that harmonizes priorities (or the needs that leverage strengths) is critical to minimizing risks, unlocking value, and creating synergies. To better illustrate this guiding principle, I offer a closer look at some of the strategic objectives associated with successful transactions:

- Draw upon scientific expertise — identify the best science in the world for the stated objective, and determine the most cost-effective solution to bring it in-house.
- Capitalize on development capabilities to reduce cost and lead time. Accelerate the discovery and development of new therapies. Deploy efficient developmental/life cycle management strategy to expedite time to market, which is particularly critical in an increasingly competitive commercial environment.
- Leverage your therapeutic footprint (including preexisting clinical and commercial expertise) to maximize asset value via enhanced execution. Accelerate commercial evolution and provide further substance and breadth to the product portfolio while reducing execution risk.
- Focus on categories/drugs with high unmet needs in areas not typically prone to innovation to expedite approval with the goal of providing new treatment options to patients.

While this expedition is not for the faint of heart, given the inherent risks and escalating price tags, it is a market reality and needs to be rationalized as a cost of doing business. With that said, developing successful strategies/approaches that minimize assumed risks will ultimately separate the winners from the losers. Like any adventure, one needs to rely on their compass: Stay true to your strategic vision while remaining grounded to the fluid competitive landscape. Perhaps it is not random that three of the hottest classes of drugs in the past two years all have competitors coming to market in tandem with the lead drug. That is, Gilead has competition already from AbbVie, with J&J and Merck still working on competitive drugs in hepatitis C; two PCSK9 monoclonal antibodies will be approved simultaneously, with a third in the mix when all report clinical cardiac reduction trial data in a year or two. The latter results will determine if these drugs sell billions; and, of course, there are two PD-1 antagonists already on the market (from BMS and Merck), each at a cost of $150,000 annually. Accordingly, one winning strategy is to find out what is hot and find a similar technology to develop, prior to me-too status. Or is this pandering to fashion?

Finally, quibbling about valuations may very well represent rounding errors in the face of success, particularly in a well-constructed portfolio approach to external collaboration. This is best exemplified by two highly acclaimed (retrospectively) transformative transactions: Gilead's aforementioned $11 billion acquisition of Pharmasset and BMS' $2.1 billion purchase of Medarex, where both carried purchase price premiums of approximately 90 percent. The latter catalyzed BMS' evolution, driven by its immuno-oncology Yervoy/Opdivo assets, which are leading an exciting new therapeutic category. Furthermore, this example speaks directly to the merits of a portfolio approach to business development; the incredible success of the Medarex acquisition more than compensated for the outright failure of BMS' $2.5-billion acquisition of Inhibitex. Bottom line: no pain, no gain, no glory. In this sport, it is either pay to play or cheer from the sidelines.

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

Advanced Technologies Cited As Essential For Clinical Trial Challenges

Clinical trials account for the bulk of drug development costs today. Electronic data capture (EDC) systems, and particularly cloud-based EDC software platforms, are recognized to improve efficiency and productivity and, therefore, decrease both drug development timelines and costs. The growing acceptance of cloud-based solutions is, in fact, reflected in the latest Nice Insight Pharmaceutical and Biotechnology Outsourcing survey results.

NIGEL WALKER
Managing Director
at That's Nice

"Cloud-based EDC systems are ideal for the complex, multisite clinical studies being performed today."

When asked which technological advancements adopted by CROs/CMOs have the greatest potential to provide cost and time savings, 62 percent of respondents indicated that cloud-based data management services are important. Mobile-based innovations for recruiting and communication with patients and mobile technology for remote monitoring were each also noted by 38 percent of respondents.

A potential outsourcing partner's level of technological innovation is one of the areas survey respondents listed as being important. In addition, they also consider the partner's use of advanced technologies to enhance safety and improve efficiency, security, regulatory compliance, patient compliance, speed, loyalty, and traceability to be important. Survey respondents also ranked quality control, R&D, manufacturing, distribution, and labeling and packaging as respectively having the greatest to least potential to benefit from technological innovation.

GROWTH OF CLINICAL TRIAL OUTSOURCING

The global clinical trial service market will reach $64 billion by 2020, growing at a compound annual growth rate of nine percent from $38.4 billion in 2015, according to Research and Markets. In addition, a U.S. Department of Health and Human Services report from July 25, 2014, stated that by 2020 close to three-fourths of clinical trials (72 percent) will likely be performed by professional CROs.

This growth in outsourcing of clinical trials is driven by several factors. First, the number of clinical trials is growing dramatically — approximately 33-fold since 2000, according to the National Institutes of Health. Second, clinical trials are becoming more complex than in the past, with many performed on a global scale at multiple sites for longer periods of time.

This growth is also reflected in the results of the Nice Insight survey when looking at the needs of emerging and start-up pharmas. More than any other activities, respondents indicated they would be outsourcing clinical research and clinical monitoring (32 and 30 percent, respectively) in the next 12 to 18 months. Biostatistics and data management also ranked fairly high, with 29 and 26 percent of respondents expecting to outsource these services, respectively. Analytical (e.g., analytical and bioanalytical testing, chemistry and stability testing, microbiology, product and particle characterization) and biomanufacturing services also ranked high, with 30 and 29 percent of participants anticipating the outsourcing of these activities.

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NEED FOR INNOVATIVE TECHNOLOGIES

In its January 2015 *21st Century Cures Discussion Document*, the Energy and Commerce Committee of the U.S. House of Representatives identified five key issues that must be addressed in order to accelerate the discovery, development, and delivery of promising new treatments and cures for patients, one of which is the need to streamline clinical trials. As a first step, the committee suggested the industry pursue broader adoption of adaptive clinical trial designs aided by innovative technologies and statistical modeling.

The July 2014 report, *Examination of Clinical Trial Costs and Barriers for Drug Development*, also determined that in addition to expanding the FDA's priority review process, the high costs of clinical trials could be reduced by leveraging lower-cost facilities and in-home testing combined with the use of mobile technologies and EDC, which were estimated to reduce trial costs from 8 to 24 percent across all phases.

Larger and more complex clinical trials generate large quantities of data that must be collected, monitored, and managed. Advanced software systems, such as Merge eClinicalOS from Merge Healthcare and BioClinica's eClinical platform, can help ensure not only efficient data collection, but also data accuracy and control. Information technology platforms with advanced data management tools provide real-time visibility combined with the ability to process, analyze, and evaluate the data and instantly share results with relevant stakeholders.

The FDA, in fact, supports the use of EDC systems because they benefit everyone involved in clinical trials, from sponsors to investigators to patients. Compared to traditional paper- and spreadsheet-based approaches, these systems provide more accurate data that can be more easily shared and monitored, and they offer increased compliance with regulatory requirements and lower overall costs. The agency also encourages the use of advanced data management tools that enable adaptive trial design, which has been estimated by the Tufts Center for the Study of Drug Development to save sponsor companies between $100 million and $200 million annually through early termination of unsuccessful studies. Such tools include cloud-based data collection and storage systems, programs that enable real-time data monitoring, data analysis tools for real-time and continual evaluation of results, and security systems for data access control, among others.

Trial planning and study build-out and start-up are also simplified with EDC solutions because it is possible to establish timelines, determine the required number of sites, and define responsibilities for different staff members across multiple sites at the outset. As importantly, there is no need to create paper case report forms (CRFs) or keep track of thousands of pieces of paper, and the data is centrally located for easy searching and analysis, which enables early identification of trends and significant outcomes. Communication among all parties is also enhanced, which means that problems are caught and addressed before they become major complications.

Several studies have confirmed the benefits of EDC systems. Cost savings have been found to result from the elimination of on-site monitoring, the reduction of the time required for cleaning up data errors, and the lowering of general processing costs (*Global Clinical Trials: Effective Implementation and Management*). In another study outlined in the 2011 Thompson Reuters report, *Information Technology Is Improving Clinical Practice*, more than 300 trial days were eliminated on average following the implementation of EDC systems.

CLOUD-BASED EDC MAKING AN IMPACT

Cloud-based EDC systems are ideal for the complex, multisite clinical studies being performed today, because all information (study protocols, patient data, images, outcomes, etc.) is stored in a central location and maintained by a third-party service provider. The data can be input from any type of Web-based device, including smartphones for easy patient reporting, and is automatically updated and collated for more rapid and efficient data monitoring. The most advanced cloud-based EDC systems also include capabilities for tracking the drug supply, managing images, and coordinating reporting, translation, patient education, and other activities that go well beyond simple data capture. Because there is no sizable up-front investment with cloud-based EDC systems, organizations of all sizes can benefit from the advantages of increased efficiency and productivity.

Today's pharmaceutical manufacturers are constantly faced with driving down costs and improving product performance (e.g., efficacy, ease of use, patient adherence). Consequently, more clinical trials are being outsourced, but at the same time, the costs associated with conducting even outsourced clinical trials have increased.

Innovative technologies that range from cloud-based data management systems to increased automation for production and analyses are, therefore, attracting significant attention, as indicated by participants in Nice Insight's survey. Cloud-based EDC systems combined with mobile and wearable technologies, most notably smartphones and smart watches to date, are beginning to have a real impact on improving efficiencies and lowering costs, and sponsor companies are attracted to CROs/CMOs that recognize and leverage such state-of-the-art data management solutions.

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

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

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GENO GERMANO
Group President of Global
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PFIZER:

A PURE POWER PLAY for INNOVATIVE PHARMA

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

A show of hands, please. How many of you reading this know about Pfizer's split into several separate pharmaceutical businesses? Just in case you missed it, on Jan. 1, 2014, Pfizer formally divided into two separate business units that together possess three different "operating segment" groups. One business unit, Innovative Products, consists of two groups: the new Global Innovative Pharma (GIP) and Global Vaccines, Oncology, and Consumer Healthcare (VOC). The other unit, Established Products, contains the third group: Global Established Pharma (GEP). Significantly, the GIP business, headed by president Geno Germano, has innovation written right into its name.

"Innovative Pharma" spotlights an area of Pfizer long obscured by a drumbeat of major acquisitions that brought with them many of the company's leading products, along with the inevitable challenges of integrating the acquired R&D operations. To outsiders, it has often looked like Pfizer, in turning again and again to M&A for new products, had virtually forfeited its own ability to innovate.

Actually, the company discovered, developed, or co-developed more than half of its current top drugs and three of its last five approved drugs. But the acquisitions tended to mask those accomplishments and amplify the contribution of acquired companies and their products. The new business groups clearly put the emphasis back on the company as an innovator.

"We wanted to create two businesses that would be market leaders in their respective categories," says Germano. "One business would be among the industry's most innovative pharmaceutical companies in certain therapeutic areas, and the other would be an established products business, with sterile injectibles, biosimilars, and emerging markets as growth engines."

Lead To Innovate

GIP, in particular, is the nexus of pharmaceutical innovation for Pfizer outside vaccines and oncology drugs, at least in "post-PoC" or late-stage development. Germano has global P&L responsibility for the GIP group, which will develop new drugs exclusively in the cardiovascular/metabolic, neuroscience/pain, inflammation/immunology, and rare-disease therapeutic areas (TAs). He says the GIP segment is strategically focused on developing, registering, and commercializing "value-creating" medicines capable of giving the company front positions in those areas.

"Our goal is to achieve leadership in each of our therapeutic categories," he says. "That is a key strategic imperative for us. By doing so, we believe we can generate superior results for the business and put it in a strong competitive position."

A team Germano co-chairs with Mikael Dolsten, head of worldwide R&D, coordinates decisions and capital allocation for research and development across the entire enterprise, he explains. "As the business-unit head, I am responsible for recommending whether to invest in the late-stage development for particular drugs, and I have a team that conducts the late-stage development."

Pfizer's portfolio has grown with the company over time. Now number one to four in the industry depending on the ranking parameter, the company was only in the mid-20s when I first visited its headquarters in 1987. Many of its current products have lost their exclusivity, however, and require much different management than newer products with their exclusivity still intact. Exclusivity status — having it or having lost it — is thus the essential dividing line between products assigned to either the GIP or GEP group.

"Before and after exclusivity, products have different levels of emphasis and priority for different stakeholders," says Germano. "Pricing and contracting strategies differ, as do operations and

cost structures. We realized that, to optimize the overall business for the whole company, we should develop separate divisions for the post-loss-of-exclusivity (post-LOE) products — about a $25 billion business — and the innovative pharma business, which involves the traditional drug development, registration, and introduction of new products, and where you invest heavily in science, building relationships with key opinion leaders, communication, and education."

GIP, like all of the segment groups, operates as an independent business with reporting of separate quarterly financials under Pfizer, though not further "externalized" on the stock market or with its own company brand. The quarterly reporting should give more transparency to the performance of the business units, according to Germano.

"One of the challenges Pfizer had was not always getting full recognition for each of the components of our business. There was one great big giant Pfizer with one number as its performance metric, and you could not really see what was going on inside. We now report to the street on the relative performance of each business, so we can engage in much deeper discussions with the investors on the future of the individual businesses. We have operated in this structure for a little over a year, and we have made significant progress in launching new products, advancing the pipeline, building commercial presence in key geographies, and managing cost structure."

Strategic partnership is still a core leverage-producer in GIP efforts to translate advanced science and technologies into new medicines, as Germano says: "We actively look to establish alliances and partnerships to develop therapeutics, expand disease biology understanding, and identify biomarkers in our areas of focus."

Triangulate Need, Skills, Science

Germano emphasizes that the therapeutic areas Pfizer has targeted for innovation are not random choices. Beginning several years ago, he says the company refined its R&D strategy to focus on therapeutic areas where it saw the triple conjunction of patients' unmet need, internal capabilities and talent, and the likelihood of scientific breakthroughs. Within those areas, however, each project must stand or fall on its own.

"We built multiple tools and metrics to help us objectively evaluate projects going through development," he adds. "We can compare them to each other in level of risk, potential value generation over time, and, of course, cost of development. Those tools helped us value the portfolio and determine which assets to take forward and which ones to discontinue or externalize in some way."

The handoff from early R&D to post-PoC development presents another useful filter in the process, in Germano's view. "This organizational structure has introduced a dynamic that compels more engagement across the R&D-business divide. It creates a point of tension and challenge that drives the research teams to communicate with the business teams, and vice versa. We together want to aim for a compound that will have the best potential for success from early stage research to development and registration."

Germano believes the reformed R&D is working out well, and he has the evidence to back him up. Pfizer has achieved 16 new product approvals in the past four years, and more than 20 positive PoC candidates, resulting in 21 Phase 3 program starts. "We've actually had a period of greater productivity than we've seen in a long time at Pfizer."

He is particularly excited about the "important breakthroughs" he sees among the recent launches, such as the oncology drug, a first-in-class cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor, FDA-approved for first-line treatment of a certain breast-cancer segment. He also lauds the company's introduction of a new mechanism to address rheumatoid arthritis, Janus kinase (JAK) inhibition, with the drug Xeljanz (tofacitinib), and he salutes the vaccines division for developing the first meningococcal B vaccine in the United States.

With what seems like a conscious intent to move beyond the legacy of company-product acquisitions, Pfizer has formalized its "pure play" in pharma R&D, seeking to create an "engine of sustainable innovation" (ESI). "We want a consistent flow of new products," Germano says. "We don't want just to buy a product or a company with products that may yield a success now and then, almost at random. When a major product loses exclusivity, we lose an enormous amount of revenue all at once. We can't make that up in the same year, even with the launch of a new product. We need to have already introduced several new products during the previous two or three years, so we can absorb these LOEs and continuously grow the company."

Invent In 3D

Beyond putting out a string of new products, or as an integral part of it, Germano believes GIP must cultivate innovative ideas and practices at every level of the organization, not only in R&D. He has established incentives and recognition activities to encourage all employees in the group to think creatively about their jobs, responsibilities, and methods. From such "aspirational thinking" will hopefully spring cultural change. "I'm trying to create a culture where every single one of my colleagues thinks of themselves as an innovator," he says.

One training program encourages employees to propose "Dare to Try" projects to address particular challenges of operating in their country or region. Variations in the adoption of new healthcare technologies and delivery methods, use of Big Data, and payer models are among many factors that demand more creative solutions.

The initiatives have ranged from innovative, outcomes-based contracting to making clinical trials more accessible by recruiting through retail pharmacy. The

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Health & Value – Look In, Look Out

Besides heading Pfizer's Global Innovative Pharma Business, (GIP), Geno Germano has another key responsibility – managing the company's Global Health and Value function – created, the company says, "to demonstrate the value of medicines using real-world data focused on ways to improve patient access and manage patient costs." The group works with regulators and payers internationally, and, it is probably fair to say, it signals a growing industry awareness and even acceptance of value-based approaches to resolving the tug of war between innovation and reimbursement.

"Global Health and Value is all about fostering understanding of the value of the drugs we have in development and in the marketplace – the role they play in managing care for patients and delivering value to payers, whether that is a government or an insurance company. There are more healthcare systems now at risk for providing care to populations, and if you're at risk, you want to know you're getting good value for your money. So it is imperative for us to have the capabilities to demonstrate value, and this is a key area for us to continue focusing on.

It will be a continuous process to work with regulators and to advance regulatory processes and again, make it easier to bring new innovations to patients, but we have seen a lot of progress. The 21st Century Cures legislation that's going through the legislative process today includes provisions for incremental funding for NIH and our industry, and Pfizer has been very supportive of this effort by Fred Upton and Diana DeGette and with the 21st Century Cures Act.

On the other hand, at Pfizer we have taken up the issue of corporate tax and how it influences American companies disproportionately compared to companies domiciled in lower tax jurisdictions in countries with territorial tax systems. It is a factor in the competitiveness of American companies and the country as a whole that we have to be cognizant of, and we are actively supportive of measures that would make the U.S. corporate tax system more competitive on a global basis.

On the payer side globally, financing healthcare, including medicines, is an enormous challenge. People are living longer, and they are experiencing more difficult healthcare problems. We've made a lot of progress on the easy ones, so now we have new and bigger problems we have to solve. So it is imperative for our industry to be effective at describing, articulating, and supporting the value of the products we bring to patients."

GENO GERMANO
Group President of Global Innovative Pharma Business

leadership team also takes on specific projects, particularly in the IT/digital arena, experimenting with meeting customer needs through crowd sourcing, social media, and other emerging options. In addition to annual awards associated with such projects, an innovation fund supplies financial support for the top projects recognized as creating an advantage for the business in the market.

As a result of ideas generated through the incentives, he says, "We have funded projects that probably would not be funded in an ordinary business — not only in the development of new products, which are critical to our success, but also the adoption of new business models and tools to communicate with key stakeholders. So the concept of innovation is bigger than just R&D for us."

There is also more to R&D than new compounds. Clinical trials have also become open ground for innovative treatment. Germano describes how his group may choose traditional versus adaptive designs for particular trials:

"If we are in a leadership position, perhaps as a first-in-class, we might take a more methodical approach to make sure we get it all right. If we're in a race with another company, however, we might look for ways we can be more creative in approaching development to give us a leg up. In any case, we stimulate our development teams to stretch their thinking and look for new, creative ways to achieve better outcomes."

Pfizer, like many Big Pharmas, keeps refining its relations with external research partners in academia and among small-to-large companies. Pfizer's Centers for Therapeutic Innovation (CTI), with four locations around the world, coordinate the academic relationships, region by region. (See also my *Life Science Leader* July 2012 article "The New Pfizer Research Strategy: Openness And Collaboration Replace The Old Imperial Model.") The company has built a team of business-development experts who can talk through the science with academic or small-company researchers, a venture-capital group to finance start-ups and early research projects, and major partnerships with established companies.

Culturally, people in small, entrepreneurial companies tend to look at Big Pharma business-development bureaucracies as towers of risk avoidance. In their view, big companies leave it to the small ones to take on the hard risk of innovation. But Germano jumps at the chance to counter that perception.

"I believe it is a myth that big companies avoid risk, and one that is not accurate at all," he says. "In fact, in bigger companies where there are more substantial resources available, we have a portfolio of risk. We invest in some very early, very high-risk-taking scientific endeavors, not only through partnerships, but also in-house. We are involved in gene therapy, CAR T-cell technology, and immuno-oncology, for example. We are looking at novel therapeutic approaches to neuroscience, one of the most high-risk areas of research today. In Alzheimer's disease, where there have not been very many real breakthroughs, we are there. We're involved in discoveries, in development, and in investments."

Germano also disputes the risk-taking stereotype of small enterprises: "While there are small companies that take a

lot of risk, some small companies take relatively little risk by focusing on an incremental innovation or small variations on existing technology."

But one reasonable risk-limiting device is to take on the biggest challenges in the areas where you are most capable of doing so. Germano observes that Pfizer has been a diverse business, marketing and developing products in almost every area at one time or another. In his view, with the areas of focus well-defined, the company is free to compete at its best and possibly lead in each of those areas.

"Creating leadership in specific categories drives much of our thinking today," he says. "In those areas, we can be at the forefront of science and with patient care, we can work together in a bigger and stronger way with partners, and we can participate in the ecosystem of care. I see our future moving in that direction where we not only have industry-leading products, but we have deep relationships, deep understanding of patient needs, a total commitment to those areas, and we realize the benefits of that in our own productivity, our ability to provide strong shareholder returns, and our success in building a growing enterprise over the long term."

Many of us who have had the luck, and the longevity, to observe Pfizer's rise to the upper ranks would like to believe it has now found a new path — one of innovation inspired from within rather than primarily purchased from without. The R&D reforms began a few years back, followed by the reorganization into GIP, VOC, and GEP, may have irrevocably committed the company to the innovative path in qualitative and quantitative ways by easing its reliance on the acquisition of mature products. Still, we have the luxury of being observers. Germano and the GIP team, along with the other segment groups, must make it happen. Good thing they seem off to a good start. L

PREPARING SANOFI FOR POST-PATENT CLIFF PRODUCT LAUNCHES | By R. Wright

Preparing Sanofi For **Post-Patent Cliff Product Launches**

ROB WRIGHT Chief Editor @RfwrightLSL

> "If you want to improve adherence and change behavior, simplicity of device and diagnostic design is a big driver and should be integrated into your drug development process."

PASCALE WITZ
Executive Vice President (EVP), Global Divisions & Strategic Development, Sanofi

Choosing to come to work for Sanofi in July 2013 couldn't have been an easy decision for Pascale Witz. After all, she was leaving a job as president and CEO of GE Healthcare's medical diagnostics business, a company where she had worked for the previous 17 years. Furthermore, Sanofi was facing huge patent cliff hurdles during this time period. Despite all of that, though, Witz saw opportunity in this position as EVP and leader of Sanofi's newly created global divisions and strategic development organization.

That opportunity was to prepare Sanofi for an unprecedented post-patent cliff drug launch schedule. Part of the rationale for hiring Witz was to bring someone from slightly outside traditional pharma with demonstrated experience in rebuilding organizations, as well as a willingness to do things differently. Here's why: Since 2009, Sanofi has had the most new drug approvals of any Big Pharma (13), according to Bloomberg analyst report. And though the organization had launched 10 products from 2007 to 2013, Witz knew this pace was likely to soon double. "We could have 18 new product launches in the next five years," she attests. While you may be thinking this a bit optimistic, consider this: In the past 10 months Sanofi has launched Afrezza (diabetes), Toujeo (diabetes), Lemtrada (MS), and Cerdelga (Gaucher disease) and is readying to launch several other products before year's end. With 37 compounds in its R&D pipeline (see table on page 35), the challenge for Witz was to build a very different organization than what got Sanofi through its patent cliff period. "During a patent cliff, your focus is on asset maximization, manufacturing cost reduction, and sales efficiency," she says. "Launching new products today requires you to think more about putting the patient first — building your solutions and offerings around their needs, and seeing how you can make a difference."

As companies continue to strengthen their biologic pipelines and payers seek to reduce costs while also improving outcomes, Witz believes patients in the near future will have even greater responsibility for managing their treatments. "Most of our new products include devices," she states, using, as an example, Toujeo, Sanofi's long-acting human insulin analog that comes in a disposable prefilled pen for management of diabetes. "Early on we focused on the [Toujeo] pen itself, but diabetics will tell you the injection is the easy part. The most difficult part is first determining the dose, which requires getting a blood glucose level."

Even nondiabetics probably consider the process of conducting a blood glucose test to be fairly common knowledge — pricking a finger with a small lancet device, obtaining a small blood sample, applying a drop of blood to a test strip, inserting the strip into a blood glucose meter, and then getting a blood glucose reading. An experienced diabetic conducts this routine multiple times a day and with probably very little thought to determine the appropriate insulin dose to self-administer. If you can imagine similar processes being applied to other therapeutic areas, you can see where Witz is going. Most biologics require delivery devices. Some even require the use of a companion diagnostic to determine if the patient is an appropriate candidate for a particular therapeutic. With the goal of providing better outcomes, it is not hard to imagine that patients will soon be using multiple drug devices, as well as diagnostics, to deliver and manage their own treatment.

Where To Begin Assessing Your Talent

For Pascale Witz, EVP and leader of Sanofi's global divisions and strategic development organization, the first place to begin assessing your people begins with human resources. "Whenever I start a new role, one of the first assessments is with the head of HR," she says. "You need someone in this position that is a strategic thinker when it comes to staffing so you can have greater focus on the business imperatives." While there are a number of assessment tools that can determine one's ability to think strategically, Witz pays close attention to how someone engages with her. "A strategic thinker is not afraid to challenge you if they think you are going in the wrong direction," she attests. "It is a bit of a gut feel, and often based on the questions they're asking me." A task-oriented HR person asks what type of people you want. Someone more strategic helps you figure out the type of people you need. Witz says to be wary of an HR individual who is too much into praising how many people he or she has hired in the past. "I'm not looking for metrics in terms of number of people," she explains. "I'm looking for experience in difficult roles. I want people who will tell me if the organization I am developing will work or not and help me to make sure the plan looks, and is, simple." One of Witz's first tasks was bringing in someone from outside of Sanofi as her new head of HR.

Another assessment conducted by Witz shortly after her arrival at Sanofi involved the people focused on product launch. Beginning with conversations among her team and then division heads, Witz soon learned that, although Sanofi did have some folks in house, the reality was that, given pipeline projections, they didn't have nearly enough people for this task. According to Witz, the initial assessment revealed there was no existing team with recent product launch experience. Witz pulled together the handful of people who did have previous launch experience so she could ascertain where Sanofi had gaps relative to its developing pipeline. "This is how we scoped the organization and concluded the jobs that would need to be created. Then we looked at who was qualified, interested, and available internally who could fill those roles prior to looking outside," she explains.

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Getting Organized Required Getting Help

The opportunity to create an integrated care initiative was one of the things that attracted Pascale Witz to join Sanofi. The EVP and leader of Sanofi's global divisions and strategic development organization believed that such an initiative required the creation of five centers of excellence: integrated patient care, patient centricity, marketing, market access, and global strategic development. When embarking on creating the market access center of excellence, which focuses on demonstrating economic value to patients, payers, and regulatory authorities for newly developed therapeutics, one thing became clear — Sanofi had a lot of different subfunctions of market access spread out across the company. Given the size of the project, Witz also quickly realized that she needed the help of someone she could trust. "I decided to hire an expert consultant who had worked in a role linked to market access whom I had worked with previously," she says. "But I also built a project team and named an internal project leader to work hand-in-hand with the consultant. I'm not a big fan of just having a completely external assessment without pairing them with somebody internal who can adjust and course correct." Witz admits to having a strong opinion on this point. "Consultants deliver based on how much you guide them. While sometimes it is appropriate to have an assessment done by somebody who is completely external, when it includes either business strategy or organizational structure, you need someone on the inside who can help open doors and guide the consultant — as well as catch any misperceptions that might begin to take shape internally."

Working together, the two began conducting a full assessment of Sanofi's market access capabilities, a process that took two months. One of their conclusions was that, in order to accelerate Sanofi's market access capabilities and make sure people were working together, they had to be unified under one global function and reporting structure. "We rewrote the health economic outcome research, the pricing, the different divisions, and the market access keys and then created a market access academy to train people so we could ramp up our market access competencies. We then put an operations team in charge of managing the training academy," says Witz.

But if better outcomes and lower costs are the goal, more devices and diagnostics aren't necessarily the solution. Research has shown that despite advances in drug delivery technologies, many patients (84 percent in one study) still do not use these devices properly. "If you want to improve adherence and change behavior, simplicity of device and diagnostic design is a big driver and should be integrated into your drug development process," says Witz.

Another driver behind Sanofi's need to change involves the role of payers. "Fifteen years ago, the route of getting an approved drug covered by insurance was much simpler and shorter," she attests. "Nowadays, the sophistication of the different payers and the complexities of getting patient access to new therapeutics have made insurance companies enormous stakeholders in the drug development process." No longer can pharma companies assume that if their drug provides clinical benefit it will be covered, and therefore, prescribed. Witz knew that for Sanofi to handle this new pharma business model while planning to launch so many new products, it would need to develop a different organizational structure, a redefined strategy, and a "much more action-oriented mindset."

To Know Where You Want To Go, First Understand Where You Are

The first thing Witz did, even before arriving at Sanofi, was learn what organizations were already in place and how they were organized. She looked at how people were organized to prepare for the launch of new products and then benchmarked that information against current industry standards and critical functions. For example, she says there are three teams required to launch new products: global brand, marketing, and market access. "At first I was doing two things in parallel — identifying what teams needed to look like and what functions I needed to have access to," she explains. "Through my initial analysis, I realized that some of these functions were not necessarily well organized for product launch or optimized to leverage all of the technologies available to make a bigger impact."

Her next step was to determine the critical priorities and timelines. Of course, one of her primary priorities was ensuring Sanofi would be ready to launch its new products coming out of development. That led to a rebuilding of Sanofi's product launch capabilities (e.g., increased patient engagement, value-driven product development, better integration of combination drug-device development), dubbed product launch excellence, in September 2013. "In October 2013 we started another project designed to define a new market access organization [a center of excellence focused on demonstrating economic value to patients, payers, and regulatory authorities]," she recalls.

Identify The Talent Gaps

To ensure the success of each of the aforementioned initiatives, Witz had to determine where there were talent gaps. She began working with headhunters and HR (see sidebar "Where To Begin Assessing Your Talent" on page 32) to develop desired candidate profiles and draft job descriptions. "Having headhunters review job description drafts can be very helpful to identify the most critical aspects of a job so you don't end up with a position that looks great on paper, yet will never be able to be sufficiently filled," she says. This exercise led Witz to conclude that Sanofi needed a new head of global market access, a new head of global marketing, a new head of strategic development, and a number of other positions. For some of the slots that needed to be filled, Witz was deliberate in seeking experience from outside of pharma. For example, when hiring for an integrated care

position, she wanted someone with experience in instrumentation, design software, and devices. "I felt neither Sanofi nor pharma had people with the level of experience I wanted in these areas," she says. "Experience, as well as having the right mix of people, matters." Other attributes of importance for Witz include leadership and the ability to come up with ideas and recommend a path and defend it. "I want people who are self-confident and can lead by example so they can shape the company by exerting influence beyond their direct team," she states.

For a newly created position, chief patient officer, Witz wanted someone who was very patient-centric and not colored by the way traditional pharma operates. "Filling this position was actually very difficult because I wanted a mindset more than a profile," she explains. "For that specific hire, I had to actually argue with the headhunter who initially wanted me to target somebody with pharma R&D experience." Though Witz conducted a few interviews with folks having this background, she found many commenting how they would be good at telling R&D how to work. "That's the last thing I wanted," she says. "I wanted someone who was working *with* R&D, *with* my commercial team, and *with* my division, not somebody who was telling others what to do." Sticking to her original plan, Witz eventually landed Anne Beal, M.D., MPH, a pediatrician and public health specialist from the Patient Centered Outcomes Research Institute (PCORI) — the United States' largest institute focused on patient-centered outcomes research. The move made Sanofi the first top 10 Big Pharma to create and fill a chief patient officer position. "I strongly believe that innovation comes from creating a convergence of different fields," she attests. "If you want to better understand the patient's perspective, bring in someone with significant patient experience. If you want to better understand how to develop combination drug devices, acquire people with device experience."

Witz shares that, though Sanofi did have a lot of very good people internally, some were not at the right level of competency. "It was more a question of training," she says. Her advice is not to compromise and place someone in a role beyond their skill level, but instead do what she did — create a mentor system to build your internal capabilities.

Another tip, don't use the same headhunter to fill every position. "When you are in a position to build the team, talk to different headhunters to tap into a variety of experiences and perspectives," she says. "A lot of the roles to be filled were going to be a part of my leadership team. For the headhunter to really understand what I was looking for required me to be quite engaged." While Witz believes that building the right team requires having an HR partner you trust, recruiting top talent is not something to be completely delegated. "There are many areas where I don't have the expertise, and I'm fine with that," she states. "My role as a leader is to be able to lead a team with complementary knowledge and skills. While this requires being able to get along with and trust the people you hire, because many positions were being filled by nontraditional pharma people, I could not just hand it over to HR and let them handle it. Even when I look back, I don't think this is something that I could really delegate as I will be relying on these people for their expertise."

Since spearheading the integration of Sanofi's burgeoning product pipeline with its product launch capabilities and its patient-centric initiatives, Witz has been very busy. In just over two years, she has successfully filled a series of key positions such as chief patient officer, head of strategic development, head of marketing, head of market access, business leaders for specialty care division and biologics division, and repositioned internal staff to gain better functional and reporting alignment. Despite all that, several initiatives remain works in progress. In order for Sanofi to achieve its goal of reflecting the future of biopharma (i.e., patient-centricity), it requires a continued focus on shifting its culture toward a model that integrates patient care with disease-specific drug/device development.

R&D Pipeline Summary Table*

Table 1

	Phase I	Phase II	Phase III	Registration	Total
Oncology	4	1	0	0	5
Diabetes Solutions	1	0	2	0	3
Cardiovascular/ Renal Diseases	1	1	0	1	3
Immune Mediated	2	2	2	0	6
Infectious Diseases	0	1	0	0	1
Ophthalmology	2	0	0	0	2
Rare Diseases	2	1	2	0	5
Age-related Degenerative Diseases	1	1	0	0	2
Vaccines	2	3	3	2	10
Total	**15**	**10**	**9**	**3**	

27

25

12

37

NMEs & Vaccines

*Excluding life cycle management programs

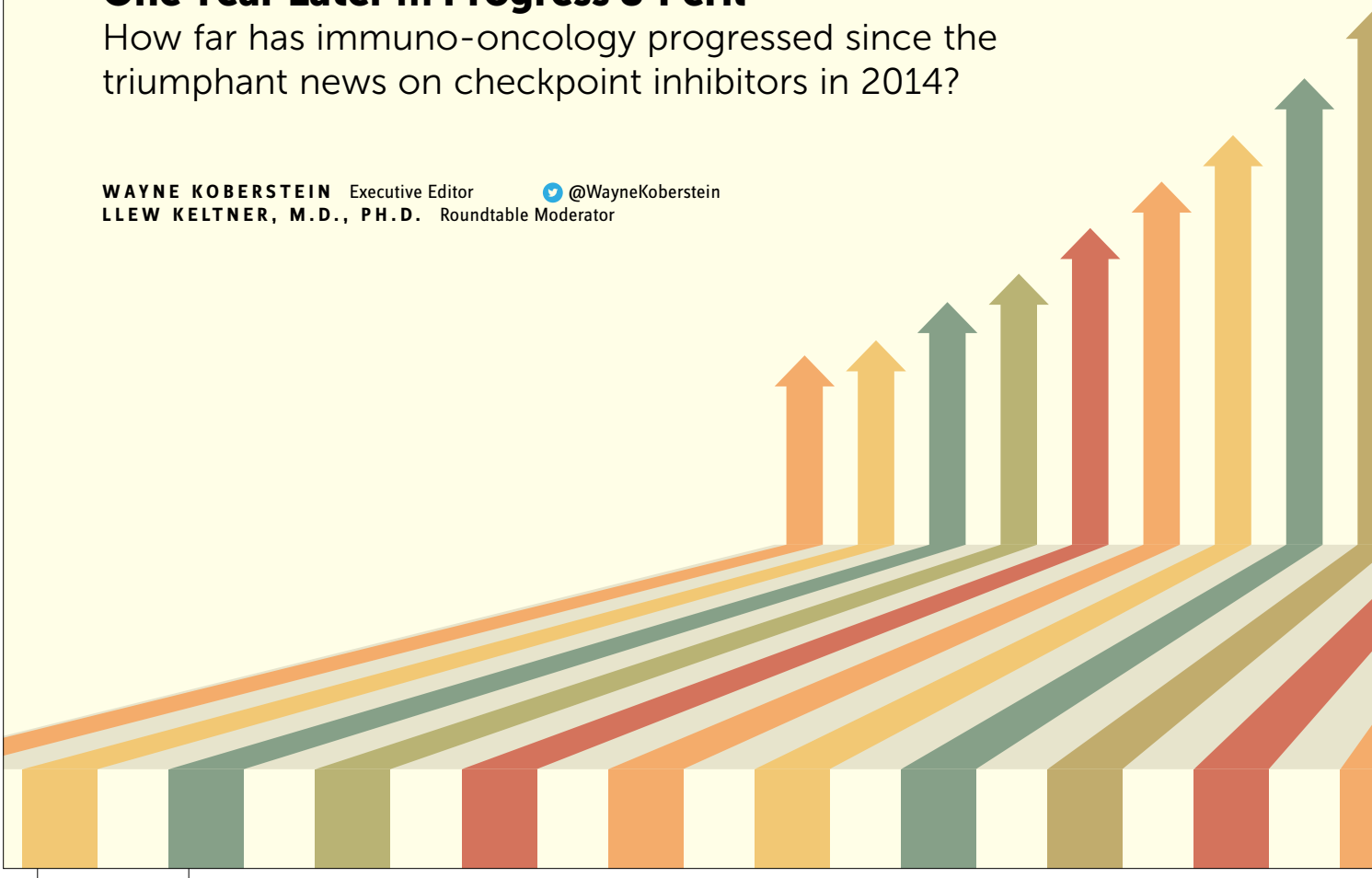
During the writing of this article, Sanofi announced a new global business unit structure. Consisting of five business units (general medicines & emerging markets, specialty care, diabetes & cardiovascular, Sanofi Pasteur, and Merial), the new structure will go into effect in January 2016. Peter Guenter, former EVP, global commercial operations, will head up the general medicines & emerging markets global business unit. David Meeker, former EVP and CEO of Genzyme, will lead the specialty care global business unit. The diabetes & cardiovascular global business unit will be led by Pascale Witz. Sanofi Pasteur and Merial will be led by their current respective leaders, Olivier Charmeil and Carsten Hellmann. The composition of the executive committee remains unchanged.

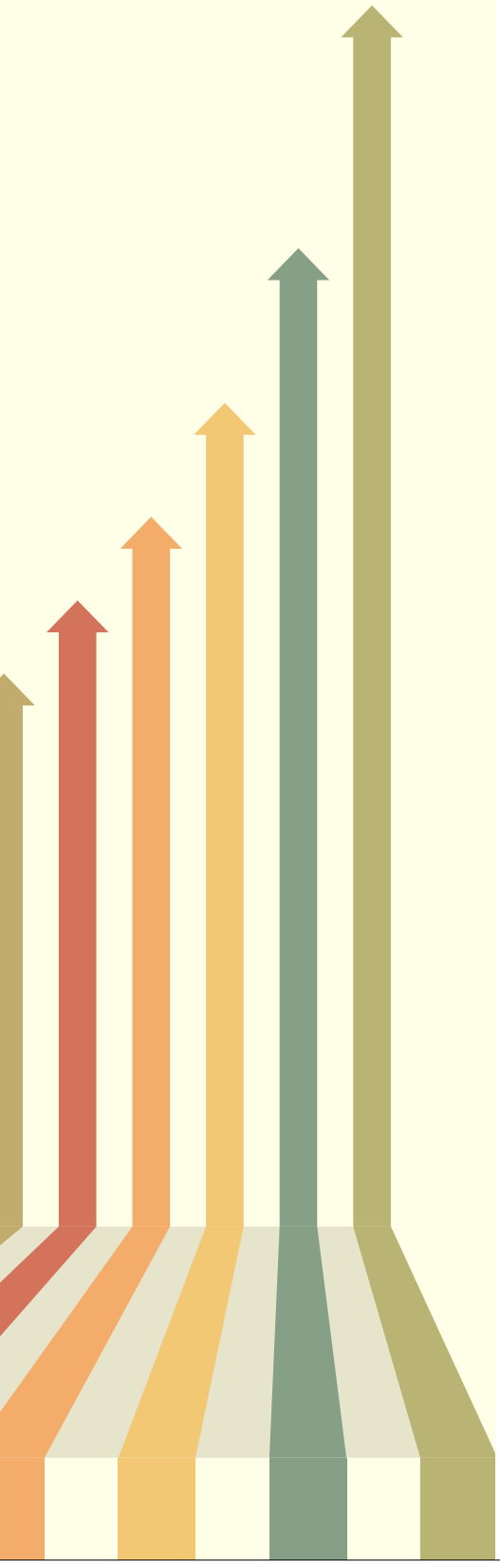
COMBINATION CANCER IMMUNOTHERAPY: A 2015 UPDATE

One Year Later ... Progress & Peril

How far has immuno-oncology progressed since the triumphant news on checkpoint inhibitors in 2014?

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein
LLEW KELTNER, M.D., PH.D. Roundtable Moderator





What a difference a year makes. Last year, beginning in September, we ran a series that addressed the challenges and opportunities of using new agents to rally the immune system against cancer. In most cases, we were talking about the checkpoint blockers such as ipilimumab and tremelimumab, inhibiting the checkpoint CTLA-4, and nivolumab, pembrolizumab, and pidilizumab, which have a multimodal effect on another target, PD-1. Checkpoints are proteins expressed on immune cells that normally "check" the immune system from attacking the body's own cells. But tumors can hijack the checkpoints to keep the immune cells inactive and thus prevent an immune response.

Just a few highlights of how immuno-oncology (IO) has progressed during the past year:

- The FDA approved two more checkpoint inhibitors: Opdivo (nivolumab) from BMS and Keytruda (pembrolizumab) from Merck, both anti-PD-1, to join Yervoy (ipilimumab), a CTLA-4 blocker from BMS, on the market.
- PD-1 became the leading target of the industry's gold rush into IO, and its ligand, PD-L1, became both the leading biomarker candidate for anti-PD-1 agents, perhaps to indicate which patients would benefit from monotherapy or a combination of anti-checkpoint agents (see next), and the second leading target of IO clinical development.
- A Phase 3 melanoma study of ipilimumab and nivolumab used separately and in combinations showed partial but durable responses in 17 percent (ipilimumab) to 46 percent (combo) of treated patients, and complete responses in two percent (ipilimumab) to almost 12 percent (combo). Substantially more patients in the combination arm had durable positive responses — with the exception of PD-L1-positive patients, whose responses were equally positive in both the nivolumab and combo rounds. But the frequency of side effects was also higher in the combo arm.
- Late-stage trials in an expanding range of solid-tumor cancers showed record-setting positive results, reinforcing the view of IO as an approach with broad, pan-cancer potential.
- More than 500 combination IO trials are likely to be running by Jan. 1, 2016, using the popular agents as well as other checkpoint inhibitors, costimulatory molecules, cancer vaccines, and immune system "conditioners" from many companies, small biotech to large pharma.

Immuno-oncology has also shown signs of a more complicated reality, as shown by the scientific debates over ideal combinations, mechanistic explanations, and other remaining challenges. Beyond the scientific questions, the world of business started to have a larger impact on the IO space during the year. More IO agents are in the running, and companies that lack them in their oncology pipelines are gold-rushing to get them. With more and more companies involved in some form of immuno-oncology, the boundaries of the field keep expanding.

Large companies seem to have the upper

hand with late-stage candidates and will inevitably and profoundly affect their clinical development, from trial design to choice of indications. Considerable angst in the research community has resulted, based on concerns that Big Pharma will waste a lot of opportunities by taking the easiest paths to market — avoiding the hard work and patience needed to develop immunotherapy to its fullest potential.

Experts Return, Experts' Turn

For this update, we brought in most of our original "virtual roundtable" experts and other key opinion leaders (KOLs) to discuss such questions as we assess how far immuno-oncology has come toward fulfilling its promise since last year. Within that circle of viewpoints and information, we take some space to comment on the wild cards in this deadly serious game of thrones building in the biopharma worldscape — the cancer immunotherapy business.

The KOLs are not just thought *leaders*; they are thought *doers*. They are some of the key researchers pushing the envelope of immuno-oncology by doing the pivotal clinical trials. They are nearly all practitioners as well, treating patients in specific cancer areas, from melanoma to lung and GI. One panelist had to put us on hold while she took a patient's urgent call.

With some exceptions, this is an unabashedly pro-immunotherapy crowd, all of them working on checkpoint inhibitors. But if you want a firsthand view of a major expedition into new therapeutic territory, you will find yourself walking alongside the lead explorers, who tend to look on the positive side of the trip.

In our live conversations with the KOLs, prepared questions often went out the window in favor of those that occurred on the spot. Yet a single question contained all: How has your perception of immuno-oncology changed in light of new research since the dramatic findings released last year? Here follow individual accounts of the experts' responses.

KOL Reflections — The Past Year In IO

JEDD WOLCHOK, M.D., PH.D.

Chief, Melanoma and Immunotherapeutics Service, Memorial Sloan Kettering Cancer Center

"The pace of progress in immuno-oncology has continued to be very brisk."

Although quick to cite other people's research, Dr. Wolchok has led or co-led some of the most important studies of cancer immunotherapy released during the past year. Foremost among the 10 trials presented at ASCO and listing Wolchok as an author is the star Phase 3 trial, "Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma." Taken together, he says, the body of research released at AACR and ASCO this year confirms the five major advantages of checkpoint inhibitors: 1) They produce the highest response rates with the longest durability ever seen. 2) They can be highly effective not only in liquid cancers, but also in solid tumors. 3) They are applicable in a growing list of cancers, confirming their broad-based mechanism. 4) Combinations can produce even greater responses, though also more frequent adverse events. 5) Toxicity can be serious but is "manageable" and less severe than in traditional chemotherapy.

Wolchok is also intrigued by results from the Phase 3 combination trial concerning PD-L1. "Patients with more than 5 percent PD-L1 expression on their baseline tumor samples had the same median progression-free survival (PFS), 14 months, whether they received nivolumab alone or the combination of nivolumab and ipilimumab. But patients who had a lower than 5 percent PD-L1 expression showed a large difference between those on nivolumab alone, with a median PFS of around six months, compared to those on the combination, with more than 11 months."

The incremental PFS benefit with the combination for patients with a less than 5 percent PD-L1 expression allows oncologists to discuss treatment alternatives with patients based on a useful biomarker, Wolchok suggests. "This carries forward into discussions of value, and we need to continue the dialogue about value. There is more to value than dollars and cents. If there are different treatment regimens with different efficacy, safety profiles, and costs, it is important to have biomarkers that may inform those decisions." He believes biomarkers may also help unravel the reasons for nonresponders, especially in cancers that have been more intractable to checkpoint blockade — as with the correlation found between response and mismatched repair protein status in the ASCO-reported colorectal cancer trial.

MARIO SZNOL, M.D.

Professor of Medicine (Medical Oncology); Clinical Research Program Leader, Melanoma Program, Yale Cancer Center

"It's not all about combinations — first of all, we are seeing a demonstration of the vast number of tumors for which a subset of patients can respond to these agents."

Mario Sznol is a leader of the recent key studies with ipilimumab, nivolumab, and pembrolizumab, including the Phase 3 trial of ipilimumab and nivolumab in combination compared to monotherapy. He says research now indicates more than a dozen malignancies respond to anti-PD-1 therapy, at least to some degree, and the responses can be durable and meaningful for a very large number of patients. But, he observes, the data on the agents is relatively quite limited.

Based on the recent research, Sznol still believes combinations can work better than monotherapy, but no single

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combination will suit everybody — or every patient subset. And for a large subset of patients, monotherapy seems sufficient, as in the case of PD-L1-positive patients treated with anti-PD-1 therapy. He maintains use of immunotherapies will improve as scientists continue to identify all of the T cell inhibitors in a tumor microenvironment and learn how to reactivate the T cells.

Sznol says the past year's developments confirm checkpoint blockade as a real revolution in oncology — not hype. In previous developments, such as anti-angiogenesis, he says, "Much of the hyperexcitement erupted before clinical data had proved the concept, but clinical data is exactly what drives the current interest in immunotherapy." Still, he believes checkpoint-related immunotherapy, however powerful, will remain only one weapon among many against the intractable foe of cancer.

On the business level, Sznol sees a potential pitfall for cancer immunotherapy. "The danger is when a large company buys a small company with a number of assets, then focuses only on the near-term opportunity, leaving earlier-stage but promising assets aside."

Despite the demonstrated importance of PD-L1, Sznol doubts any one receptor or gene can function as a reliable biomarker for cancer immunotherapy. "The biomarker world is much more complicated — this is not like a mutation that predicts response to a drug. The immune response is complex here, involving characteristics of the tumor and of the immune cells trying to attack the tumor. There are so many variables, it's hard to believe that we can look at just one or two of them and predict what the outcome will be."

TIM F. GRETEN, M.D.

Head, Gastrointestinal Malignancy Section; Senior Investigator, Thoracic and Gastrointestinal; Oncology Branch, Center for Cancer Research, National Cancer Institute

"After the initial hype, people are starting to realize that maybe immunotherapy doesn't work as easily as we initially thought — something I have anticipated."

Tim Greten is an immunologist who cheers the ascent of immuno-oncology, but just as he reveres the power of the immune system to heal, he respects its potential for destruction. Along with the stunning responses and relative safety of immunotherapies compared to chemo or targeted therapies come complex questions about their uses and effects.

The other glaring reality in immunotherapy is its failure to help a large number of patients, especially in certain cancers. Greten says immuno-oncology brings two different camps together — the oncology community and the immunology community — and it will take time for oncologists to understand how immunology works in cancer. In our series last year, Greten worried about how immunotherapy combinations may be tested. "My fear is, if you only combine checkpoint inhibitors with other immunotherapy agents, it may actually lead to premature negative data because there is insufficient immunological understanding behind it."

Checkpoint inhibitors have shown only minimal results in colon cancer, but Greten helped lead the "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency" study reported at ASCO, to explain why some colon cancer patients do benefit from PD-1 inhibition. Results suggest mismatch-repair deficiency in colon tumors could be a reliable biomarker for predicting which patients have the best chance of success with anti-PD-1.

In other cancers, he agrees the current question is whether to treat with anti-PD-1 alone or in combination with a CTLA-4 or other checkpoint blockers. The leading contender as a patient-selection biomarker is PD-L1, which Greten believes may weigh in favor of the combination option. "With a second agent, you may actually shift patients from a PD-L1 negative status into a PD-L1 positive status, and then they can be responsive to immunotherapy, which they would not have been without a combination treatment."

LAWRENCE FONG, M.D.

Professor, Department of Medicine (Hematology/Oncology), UCSF

"If anything, there is an even greater enthusiasm in the field of immuno-oncology this year."

Dr. Fong believes cancer immunotherapy is now well on its way to use as first-line treatment for nearly all major cancers. "It has been borne out in the recent studies that these drugs work in a whole host of different cancers, so their uses will be very broad. And we also have new studies showing combinations of immunotherapies, including some with targeted drugs such as BRAF inhibitors or even chemotherapies, can boost responses even more. That makes this class of drugs very revolutionary — they will redefine the standard of care as frontline therapies."

Fong served as a discussant during an ASCO presentation of a Phase 1/2 trial pitting nivolumab against hepatocellular carcinoma (HCC). Liver cancer has only one approved treatment, Bayer's Nexavar (sorafenib), a drug prone to serious adverse effects and one that tumors quickly come to resist. Even in the limited pool of 42 patients, nivolumab treatment showed significant responses: more than a 30 percent tumor reduction in 19 percent of patients (eight), lasting more than 12 months in four patients. Overall survival (OS) was 62 percent at 12 months. In comparison, with sorafenib only 2 percent of patients have the same objective tumor response, and the average OS is 10 to 11 months.

Liver cancer patients in clinical trials tend to be among the sickest, often diagnosed with late-stage disease and treated first with chemotherapy. "We still don't know whether it would be better if we treated patients with immunotherapy earlier, but the important point is, even when patients have advance disease refractory to chemotherapy, they still can respond to immunotherapy," says

Fong. "We need a push to move immunotherapies earlier and earlier in the disease state. Already, many companies are migrating their immunotherapies from 'chemotherapy refractory' and all other 'treatment refractory' indications to first-line treatment in the metastatic setting."

SUSAN F. SLOVIN, M.D., PH.D.

Attending Physician, Member Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center; Professor of Medicine, Weill-Cornell Medical College

"Provenge really revolutionized the prostate-cancer field and brought back immunotherapy. Nevertheless, the enthusiasm was dampened when we didn't see robust antitumor responses."

Although Dr. Slovin is a believer in immunotherapy, the actual experience with the new agents in clinical trials in her field has made her more circumspect about the field. So far, only Dendreon's cell therapy Provenge (sipuleucel-T) has had clearly positive results, though nowhere near matching the durable response rates checkpoint inhibitors have shown outside the prostate. Ipilimumab has shown only marginal effectiveness, producing durable responses in a handful of patients. Why should prostate cancer apparently fail to yield to the same treatments achieving record responses in other cancer types?

Slovin lists three possible reasons: 1) standard trial designs may give checkpoint inhibitors insufficient time to produce an immune response and/or antitumor effect; 2) prostate cancer may be less immunogenic than other solid tumors, i.e., prostate cancer is not hypermutated as other solid tumors such as melanoma, renal cell, bladder, or lung cancers; 3) the bone trophic nature of prostate cancer may make it difficult for immune cells to get to sites of disease in bone. A fourth reason could help explain the lack of evidence for effective checkpoint blockade in the prostate: Companies developing these new drugs are running very few trials in prostate cancer compared to others, based on their perception

of relative risk and potential lack of a signal of activity.

Slovin's own research focuses on the scientific explanations for the prostate exception, especially on the mechanisms involved in reasons 2 and 3, above. She and a colleague are investigating the "tumor-stromal interface," where T cells try to enter the tumor but fail to do so. "There are inhibitory factors on fibroblasts, such as the CXCR [chemokine (C-X-C motif)] family, that may be prohibitory or inhibitory to T cells getting across that interface," she says. Her team has developed a CAR-T procedure that engineers each patient's own T-lymphocytes to target and destroy prostate tumors by recognizing prostate-specific membrane antigen (PSMA) expressed on the tumors' surfaces. She says GU (genitourinary) oncologists are also anticipating results soon from the completed PROSPECT Phase 3 study on Bavarian Nordic's Prostvax DNA vaccine.

MICHAEL A. POSTOW, M.D.

Medical Oncologist (Melanoma), Memorial Sloan Kettering Cancer Center

"Everyone was always hopeful that someday immune therapy would be fruitful for patients with cancer, but when the checkpoint antibodies came forward with such efficacy, we gained a whole new expanded horizon for what is possible."

Dr. Postow is involved in numerous immunotherapy trials in melanoma and, like other researchers, has seen its benefits manifested in his own patients. "In my opinion, it is now firmly established that PD-1 is a frontline treatment option for patients with melanoma, in most cases," he says. But he is also impressed with immuno-oncology's progress outside his own area. "Many different tumors that were not believed to be immunogenic are now responding to therapies, and that's leading to better outcomes overall, everywhere across oncology."

Postow cites big improvements in overall survival with anti-PD-1 drugs in melanoma and lung cancer, the high-response rate to anti-PD-1 by mismatch repair-deficient tumors, and the expanding list of tumor types showing response to anti-PD-1 or anti-PD-L1 antibody approaches. "That anti-PD-1 continues to demonstrate improvement in overall survival, and the superior response to the combination of ipilimumab and nivolumab, set the stage for the whole ASCO meeting by putting immunotherapy in a new context."

Involved in numerous immunotherapy trials, Postow authored the article, "Managing Immune Checkpoint-Blocking Antibody Side Effects," published in the ASCO Meeting Proceedings, which puts the immune-related side effects in context and recommends a number of countermeasures. He believes immunotherapy safety will continue to improve with practice, experience, and increasing knowledge.

Prospects for nonresponding patients in checkpoint blockade should also improve via mechanistic discovery and ancillary development, in Postow's view. Echoing other experts, he says, "There are no T cells in certain tumors, and some people believe the lack of T cells in tumors might be a reason that patients don't respond. Therefore, finding ways to bring more T cells into the tumors is one hypothesis of how to increase the response rates for these agents."

PAM SHARMA, M.D., PH.D.

Scientific Director, Immunotherapy Platform, and Professor, Departments of Genitourinary Medical Oncology and Immunology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

"It's becoming more and more clear that combination immunotherapy definitely has a role to play."

Dr. Sharma, who works closely with Jim Allison and the team that discovered and developed the CTLA-4 blocker ipilimumab, is referring above not just to combinations of checkpoint inhibitors, but also combo regimens including radiation, chemo, and targeted therapies. She cites the Phase 3 combination study in melanoma for showing a significant boost in benefit for patients taking both ipilimumab and nivolumab and for pointing to the importance of using biomarkers such as PD-L1 expression to guide treatment with monotherapy or combination immunotherapy rather than using PD-L1 expression as a biomarker to include/exclude patients for treatment with immunotherapy.

"Combination therapy is definitely playing out the way we had thought it would," Sharma says. "Some people had been very concerned about the toxicities, which are turning out to be manageable. There were no deaths reported as a result of the combination therapy with ipilimumab and nivolumab, and the added toxicity was in frequency, not type, of adverse events." She does believe, however, that the higher number of adverse events in the combination arm may suggest a limit to how many agents of the same type should be used together. She points out that side effects with chemotherapy are also frequent but manageable, though the highest percentage of patients reporting side effects in this trial was 55 percent in the combination arm and 16.3 percent in the nivolumab monotherapy arm.

Sharma believes converting nonresponders to responders will come with better combinations that make tumors more vulnerable to immune attack. "We are learning that it is possible to get immunotherapy to work even in patients with lower mutational load, as in kidney or prostate cancer. You can drive and sustain T cell infiltration in a combination therapy setting. Combination immunotherapy can give us the possibility of moving all the tumor types into the realm of clinical benefit."

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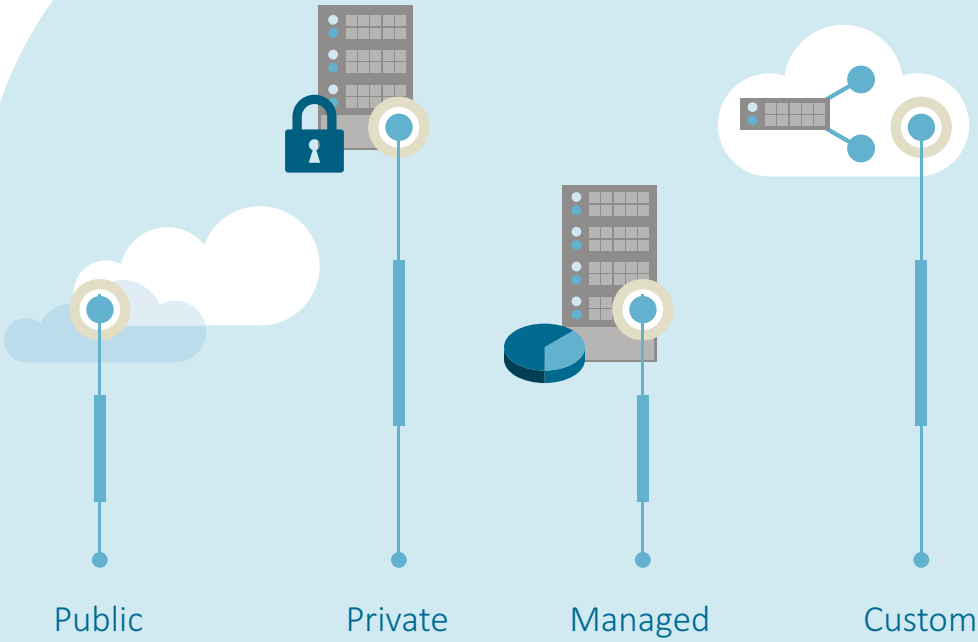

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FORESEEING STRIFE: THE MODERATOR'S VIEW

Llew Keltner, M.D., Ph.D., president and CEO, Epistat, served as inventor and moderator of our Combination Cancer Immunotherapy Virtual Roundtable. In his comments to follow, Dr. Keltner looks beyond the current focus on checkpoint inhibitors and raises issues the IO (immuno-oncology) community will be forced to address as the present euphoria fades:

It is now more obvious than ever that IO will be the mainstay of cancer therapy in the future. The major issues are not now technology or clinical benefit, but reimbursement and implementation of combinations by Big Pharma. Most large companies are doing very little, as predicted, to address the repercussions of introducing multiple, highly expensive drugs for combination IO therapy. So the payers and buyers are making decisions on their own about what they will and will not support. Concern about cost also reverberates throughout the IO research community; all of the experts in this report have echoed it. The industry can either cooperate on this issue and build real, long-term patient and corporate value or head down a path of perpetual conflict and major detriment for the most-needy patients.

The future of IO depends on getting pivotal combinations of diagnostic and therapeutic technologies into the right studies, especially innovations that will allow activation of multiple critical immune pathways in single drugs. For example, Heat Biologics recently released animal model data on its combination of a validated cancer vaccine and a costimulator in one drug. Without a functional population of antitumor memory CD8 T cells, a checkpoint inhibitor has little chance of efficacy. The opportunity lies in brilliantly combining drugs from the three classes of IO MOAs (mechanism of action): checkpoint blockade, vaccination, and costimulation.

Meanwhile, unfortunately, many of the combinations adopted due to the cash-driven rush to commercialization may be wrong for patients. Combinations of checkpoint inhibitors, including the combination of ipilimumab and nivolumab noted by the KOLs, certainly appear to yield startling responses for subpopulations of patients — but still leave many patients without adequate clinical benefit. However, the promise of combining multiple IO methods of action — checkpoint inhibition; initiation of tumor-specific CD8 T cell populations via vaccination or ablation; co-stimulation with TNF receptor superfamily agents such as OX40, GITR, 4-1BB, and TNFRSF25; and conditioning of the T cell response via inhibition of TGFß, phosphatidylserine, or tryptophan pathway mediators or addition of IL-10, IL-2, or IFN gamma — has not been fully explored clinically, yet is supported by a great deal of rapidly emerging in vitro and in vivo experimental data. New preclinical data even suggests it may be possible to bypass checkpoint inhibition entirely with combinations of the most effective vaccines and superior costimulatory molecules. But there is really no good evidence to support combining IO drugs with non-IO drugs as a preferred treatment method versus using intelligent IO combinations.

The real impediment to IO progress is not the science but the business. Many of the large pharmas are driving IO drugs through their pipelines in chaotic, almost random, fashion, defined by political and business considerations, not patient benefit. Creative research to build technical solutions to the huge looming reimbursement disaster for IO are being explored primarily only by tiny start-ups.

There is a strong tinge of desperation in some of the trials pharmas are attempting with immunotherapy in combination with ancient targeted therapies. These trials and the scattershot studies of every imaginable or purported IO agent in combinations are creating a great deal of confusion for clinicians, the market, and for patients, making it easier to cling to PD-1/PD-L1 as a de facto core for IO. But in at least one sign of progress, the past year has seen the disappearance of effective arguments for single-agent immunotherapy. Combinations are the future.

JILL O'DONNELL-TORMEY, PH.D.

Chief Executive Officer and Director of Scientific Affairs, Cancer Research Institute

"The immune system's response to cancer is multifold. You have to generate cancer-specific T cells, which requires processing and presentation of cancer-specific antigens."

Dr. O'Donnell heads a nonprofit organization, the Cancer Research Institute (CRI), dedicated to immunological approaches in oncology for the past six decades. She concurs that combinations of immunotherapies will soon be standard, first-line treatment for most cancers, though she notes some patients benefit from monotherapy with anti-PD-1 — and many others do not benefit from combination or single-agent therapy.

"In the majority of cancer types, it is still a minority of patients responding, but when they do respond, they respond very well and very durably. We need to do a great deal more research to obtain a mechanistic understanding of why there are responders and nonresponders and a practical understanding of how to convert nonresponders to responders. That will require more basic research and clinical research, which are where CRI has a role to play and where we are focusing."

Along with many of the other experts here, O'Donnell is ecumenical in considering all the possible combinations — including IO agents with chemo or targeted therapies. "The T cells have to traffic to the tumor site and infiltrate the tumor bed, which is an immuno-suppressive environment. In the patients who respond well to checkpoint inhibitors, the tumors are not presenting any other obstacles to immune response. But in the nonresponders, there are obviously negative regulators stopping the T cells from functioning. Our challenge is to understand how we can inhibit the negative factors and increase the positive factors." L

And in the future, please watch for periodical updates in "Spotlight on Immuno-Oncology" – interviews, commentaries, and analyses of key developments and issues in the IO space.

How Social Media Might Be Sabotaging Your Clinical Trial

ED MISETA Executive Editor @OutsourcedPharm

In many ways, social media has been good for the advancement of clinical trials. It is an effective way for pharma to find and recruit patients, make patients aware of trials, and even educate the public on the benefits of trials. It has also become an efficient way for pharma to interact with patient advocacy groups.

With the numerous groups that now exist for patients with almost any disease or ailment, reaching and interacting with those groups and building lines of communication with them has never been easier.

But for those conducting clinical trials, there is also a dark side to social media. While not a new trend, it is certainly one that is growing and has the potential to impact trials in a negative manner. The problem is study participants taking to social media to discuss their trials, symptoms, and trial medications.

Years ago, it was not possible for patients participating in studies to easily communicate with each other. Even if you had two patients in the same city participating in the same study, it would have been difficult, if not impossible, for them to connect. Social media has quickly changed that. Three trial participants as geographically dispersed as CA, FL, and VT (or even across the globe!) could easily join a discussion group, chatroom, forum, or message board to immediately share details of their trial experiences.

There are certainly advantages to patients having these conversations. Social media provides patients an outlet to discuss their condition with other patients going through the same experience. This helps them feel they are part of a community and can help with retention by strengthening their ties to the trial. However, problems arise when those same patients start discussing aspects of the trial that have the potential to cause patient dropout, introduce bias into the study, or derail the trial altogether.

AM I TAKING THE DRUG OR THE PLACEBO?

Dr. Lindsay McNair used to be naïve regarding the information that trial participants were sharing on social media sites, but she is now very well-versed on the topic. McNair is the chief medical officer and president of consulting services for WIRB-Copernicus Group, a provider of regulatory and ethical review services and software to support clinical research. She also has spent a significant amount of time in pharma performing research and getting feedback from patient communities.

Several years ago when she worked on the sponsor side of the industry, McNair was medical director of her company's Hep C programs. She was in the process of wrapping up the first of two large Phase 2b studies and starting the second one. One day an investigator called her and asked if she had ever been on the website MedHelp. She had not.

Turns out the site had a Hep C chatroom containing numerous message threads from patients involved in the study. What McNair saw in those messages shocked her.

"I saw posts between subjects in the same clinical study talking about what their pills looked like," says McNair. "They were also trying to guess who was on the placebo and who was on the active drug based on the taste of the pill. This was a blinded study where no one knew who was getting the new drug. Yet here were patients describing whether or not their pill tasted bitter or neutral and cross-

referencing that information with what they learned from other trial participants."

Some participants were asking others about the physical characteristics of the pill they were taking, including the texture and how it reacted when it got wet. Others shared the lot numbers on the packages they received. In an unrelated study, she learned patients went so far as to crush pills and post pictures of what they looked like in powder form.

"This was a deliberate attempt by study participants to basically unblind themselves," notes McNair. "Our fear was that once a participant determined they were not on the new drug, there would be little incentive for them to continue with the study. I also saw conversations between subjects regarding side effects. There was talk of side-effect reporting and side-effect management, with some participants actually giving advice on what side effects patients should report to the investigator and which ones they shouldn't, lest they risk being removed from the trial."

I'M NOT A DOCTOR, I JUST PLAY ONE ON CHAT BOARDS

If you are concerned about this data being shared, then you better sit down, because it gets worse. One patient noted they had developed a rash but didn't want to report it. They felt it was caused by the active drug, but since it seemed to be helping with their condition, they didn't want to risk losing access to the medication. Another patient, who actually stated he was not a doctor, described in great detail how to start on steroids, do the prednisone taper, visit a dermatologist, stop the study drug, try Solu-Medrol if the steroid doesn't work, and then eventually restart the study drug.

McNair mentions one final bit of information she discovered when researching the comment threads. In the study, participants were blinded to their own HCV (Hep C virus) viral loads. The new drug would give a very different antiviral response profile than the standard of care. The viral load in a patient would drop much more quickly if they were on the new drug. If participants in the study knew they had an undetectable virus between weeks two and four, they were most likely on the new drug. To her surprise, individuals in the Hep C chatroom were advising patients to visit their primary care physician and have their viral load checked. If it was not undetectable by the second week, they were likely not on the new drug and should probably just drop out of the study.

To make matters worse, most of the participants in these chatrooms are anonymous. Therefore, there is no way to know if the individuals making the comments are reporting factual information, if they are with a competing com-

"I saw posts between subjects in the same clinical study talking about what their pills looked like."

DR. LINDSAY MCNAIR
Chief Medical Officer, President of Consulting Services, WIRB-Copernicus Group

pany, or if they are even involved in the study. It should come as no surprise that financial analysts also troll the chatrooms, so as to make predictions on the success or failure of a trial and the stock price of a company, before the trial results become public.

HOW DO YOU AVOID THE PITFALLS?

Recognizing that these scenarios do exist is just the first step toward rectifying them. The next step is determining the right actions to take. Craig Lipset, head of clinical innovation at Pfizer, admits there is no easy solution. "The social media genie has been out of the bottle for quite a while now," he states. "Patients trust other patients and want to learn from their experiences. Even when patients wonder whether or not they should be having those conversations, the feeling is that we are all human beings. It would be difficult for a patient to not share their experiences with others who are in the same position."

Lipset concedes that if pharma is using online groups and websites to engage patients, those participants will already be Internet-savvy, and the industry would in fact be encouraging those conversations to happen. "It is paradoxical to use the Internet and social media to discuss studies and increase participation rates and then tell patients not to talk about the trial while they are participating in it," notes Lipset. "Many patients will actually feel a social obligation to share their experiences with others in the community."

Lipset references the rule of 9's that exists in social media. It states that for every patient who writes a blog post, nine patients will share it and 90 will end up reading it. That's a lot of interactions to have to manage, and the implications of those conversations will carry over into recruitment, safety, and reporting. But if patients won't change, the industry (sponsors, CROs, and researchers) will have to. One approach would be to make the subjective criteria used in studies a bit more rigid and objective. For example, if one person shares that they got a headache from taking the medicine, others might say they got a headache too, even if it had nothing to do with the trial. Focusing on symptoms that can be easily checked or measured would solve that problem.

"Researchers will need to recognize that patient conversations will take place," notes Lipset. "The industry cannot keep patients from talking to each other and sharing information. It's time to acknowledge that in the trial planning stage and take necessary steps to ensure these actions will not impact trial results. A few simple steps would be to ensure the two medicines look the same, have the same feel and texture, and do not have a different taste."

A FEW ADDITIONAL CONSIDERATIONS

Lipset believes better education and communication can also minimize the negative impact of trial discussions. Educating patients on adverse trial consequences and raising their awareness of issues that could arise when discussing their experience is a first step. This type of effort would certainly get the attention of those who are concerned about the integrity of the trial they chose to take part in. Of course, you might also be opening a Pandora's box of issues by making more naïve patients aware that those conversations exist.

Companies can choose to simply ignore the conversations. But doing so ensures the conversations will continue and the risks go on accumulating.

Some companies may go so far as to actually create their own online communities for patients to communicate. This allows sponsors to also participate in an open and transparent manner and to step in and intervene if those conversations become inappropriate. The downside is that patients may not speak as openly and honestly if they know the conversations are being monitored. Additionally, there is still no guarantee those same conversations are not taking place elsewhere.

While there is no absolute solution to this problem, there are some things sponsors should be considering. "At Pfizer, one direction in which we are leaning is around the notion of a risk calculator," says Lipset. "Not all studies have the same risk stemming from social media interactions. Some communities are very active and engaged, such as Hep C and multiple sclerosis. But in other communities these types of social media interactions are quite rare."

Different protocols also will have varying amounts of risk associated with them. Lipset concludes by noting that some protocols will carry higher risk because of a more subjective endpoint, whereas others might entail a more measurable diagnostic test. "Understanding the risk level that can be assigned to different trials will allow researchers to focus their efforts on the ones with the highest risk," he adds, "and then take actions that will help to mitigate it."

As patients get more familiar with social media, opportunities are created that can be leveraged by pharma. Patient insights can be used to better plan and design studies, understand patient tolerance for the complexity that exists in a study, discover trends related to study recruitment, and understand how we can optimize endpoints to make them more meaningful to patients. The challenge for pharma will be to benefit from the good while lessening the negative impacts as much as possible.


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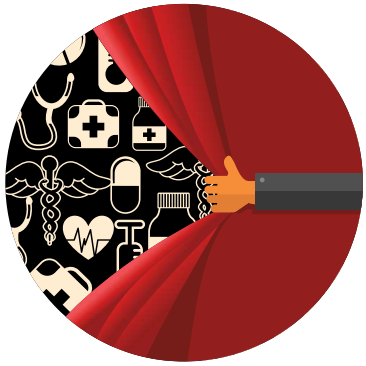
A Behind-The-Scenes Look At The Patient Clinical Trial Experience

ROB WRIGHT Chief Editor @RfwrightLSL

"When I got ill, it was completely by surprise," says Dr. Jan Vesseur. The former general practitioner who now works as a civil servant for the Netherlands Ministry of Health was on a skiing trip in France when a fall forever changed his life. "My daughter, also a doctor, was with me," he recalls. "The fall was very soft, and we couldn't believe it was anything other than some low-back pain."



When he got back to the Netherlands, he visited his physician, who referred him for an X-ray. "That was the first time I saw the broken vertebra, and that was almost a week after I fell." Ironically, it turns out having a broken back would be the least of his concerns. For within the damaged vertebra, there was a tumor, multiple myeloma. "I had to decide about two treatments, one for the spine and one for the cancer," he states. According to Vesseur, most people with multiple myeloma are diagnosed after a few years of minor complaints (e.g., tired, some back pain), with most doctors finding nothing. "No one thinks about examining the M protein [monoclonal immunoglobulin] that is the marker for this disease," he states. Due to the fall, Vesseur was fortunate to find out that he was in the very early stages of his illness. Despite being a healthcare provider, he admits that, prior to the diagnosis, he knew a little about multiple myeloma, but not the details, and definitely not *all* the possible treatments. While he explored his options, Vesseur was approached by his oncologist about the possibility of something he had never previously considered — participating in a clinical trial.

For the biopharmaceutical industry, the clinical trial is the backbone of its R&D engine. Despite the U.S. pharmaceutical industry spending nearly 40 percent of its collective clinical trial budget on patient enrollment, recruitment and retention for trials has been declining. It is estimated that nearly two out of every 10 trials never manage to enroll a single patient. Would you be surprised to learn that only 3 percent of cancer patients like Vesseur, a pretty highly motivated group, participate in clinical trials? To reverse this trend, biopharma has adopted the concept of creating patient-centric clinical trials. This model supposedly only initiates a trial site after at least one interested, pre-identified patient is found. One of the stated benefits of this model is that the trial sponsors can avoid the cost of establishing a site that may never enroll a participant, and thus are better able to funnel resources to more worthwhile study centers. The fact that the focus remains on how the sponsor will benefit makes me wonder if this approach is missing the patient-centric point. I recently interviewed three people, including Jan Vesseur, about their decision to participate in a trial/study. What follows is a look into their firsthand experiences.

THE "SUBJECT" OF A MULTIPLE MYELOMA TRIAL IN THE EU

At the time of his diagnosis, March 2012, Jan Vesseur was a 60-year-old married father of three. The standard therapy for his condition is to start chemotherapy, and after that, get a stem cell transplant. The clinical trial Vesseur was considering involved the use of bortezomib for the treatment of multiple myeloma without

"I will take part in a trial again, because I know the relevance of participating."

DR. JAN VESSEUR

stem cell transplantation. "There were two arms in the study, one with the stem cell transplantation and one without. I hoped I could get the arm without the stem cell transplant. My thinking was that if I reacted well on the drug, a stem cell transplant would not be necessary. If I didn't do well on bortezomib alone, I could always leave the trial and still get my stem cell transplant." In his opinion, the trial gave him the opportunity to get better treatment for his illness.

Vesseur's decision to participate in a clinical trial first involved a lot of reading and research as well as giving an informed consent. "They gave me a lot of paper information about the trial. Even for me, as a physician, it was very difficult to read and understand." Vesseur consulted with his oncologist and even some former medical colleagues. "Still, I didn't feel like I had all the information, and it was very difficult to foresee all the consequences of deciding to take part." Ultimately, he chose to participate in the trial, due in part to the fact that he felt his treatment and the development of his illness would be followed more closely as a result of being part of a trial.

Vesseur doesn't view his trial participation as burdensome. "Undergoing blood and bone marrow examinations were a normal part of therapy," he says. "Though they warned me that, due to the trial, I would have more bone marrow aspiration than normal, I saw this as a benefit because it would give me more information about the status of my disease. However, I can imagine there are a lot of people who have problems with having more aspirations of the pelvis, because it is a very painful examination."

Vesseur liked to bicycle the 8 kilometer (5 mile) round-trip to the hospital for treatment until he began to develop some severe side effects from the medication. "My blood pressure was very low due to autonomic neuropathy," he says. "It was so severe that I had to stop the trial, unfortunately, in November 2012." Vesseur was switched to another therapy and did end up receiving a stem cell transplant. But what he didn't receive after being forced to withdraw from the investigation was any follow-up — *ever*. "While in the trial, I felt I was well-informed about the trial and what would happen," he explains. "After I left the trial, I never heard anything and got no information at all about the results or about the effects of this treatment. I think that's not good for the motivation of patients to want to take part in trials, not at all." Vesseur believes patients should be informed about the development of the investigation, as well as the results, and in words a patient can understand. "Nowadays, trial results seem only to be published in scientific magazines for doctors," he contends. "As a trial participant, you get the feeling that you are a subject to be investigated on, not that you are taking part in a very important development for medical science. There should be more respect for the patient and the information and data they give to investigators, so an article can be written for the patients' sake as well." Though he finds the lack of respect discouraging, he doesn't view it as reason enough to never take part in a trial again. "I will take part in a trial again, because I know the relevance of participating," he states. "I'll stimulate other patients to also to take part. It's important." He suggests biopharmaceutical executives involved in clinical trials ask patients who have experience with the illness for help with trial design, specifically digging into the consequences certain trial designs have and the burden these may cause for patients. In addition, Vesseur feels inclusion and exclusion criteria should be reevaluated. "As a patient, I think they exclude much more

than we'd like, especially with cancer therapy," he shares. "A lot of researchers exclude people over certain ages or younger than certain ages, and so on, and that enormously narrows the focus of a trial."

THE PLACEBO "DO-OR-DIE" TERMINAL DISEASE DECISION

It all started with a cough for 65-year-old Laura Roix, a health-conscious power walker at the time. She was diagnosed with pneumonia, which she had endured before, but this time she could tell something was different, so she decided to see a lung specialist. "Both of my parents died of lung cancer," she reveals. The specialist told her that despite some scarring in the bottom part of her right lung, it wasn't anything to be concerned about. Four years later in 2010, the specialist informed Roix that the scarring had moved and was starting to spread. "But again, he told me not to worry," she recalls. By October 2012 she had gotten worse, having difficulty walking very far without coughing. She went searching for another doctor and eventually ended up with a new pulmonologist who did a biopsy of her lungs and determined she had idiopathic pulmonary fibrosis (IPF). Roix researched the disease and surprisingly learned from Google — not her physician — that IPF is a terminal illness. "According to the Internet, I had three to five years to live," she relates. "I went to sites like PatientsLikeMe and Inspire, where people on each told me to get to a research hospital." Living in Connecticut, Roix went to Yale-New Haven Hospital.

At the time (2013), the only treatment for IPF was a lung transplant. Thus, when Yale researchers asked her if she would be willing to participate in a clinical trial, she said "Absolutely." She was offered three different trials to choose from. "I am involved in the clinical trial, FibroGen FG3019-067," she states. "It began in 2013, and according to the ClinicalTrials.gov website, is supposed to conclude around February of 2017." Roix shares that FibroGen is an infusion that is supposed to help slow down the fibrosis process. "I go to Yale every three weeks to get an infusion via an IV in the arm," she says. "It takes about 2-1/2 hours. I was in the first phase of a double-blind trial." As a result, for the first 16 infusions, which took place over a 45-week period, Roix didn't know if she was getting the placebo or the actual medication. As of January this year, Roix has been participating in the open-label portion of the clinical trial. So for the next 16 infusions she is getting the actual drug, as long as she remains stable or gets better. "If I progressively start to get worse, then I will be taken out of the trial," she laments. "But so far, so good."

Roix has no idea if she was previously getting the placebo or the actual drug. "I did ask if that's something I would eventually find out and was told probably not," she shares. When asked if the possibility of being on a placebo was a discouraging factor to her possible participation, she says no. "At the time, there was nothing else out there, so it was do or die."

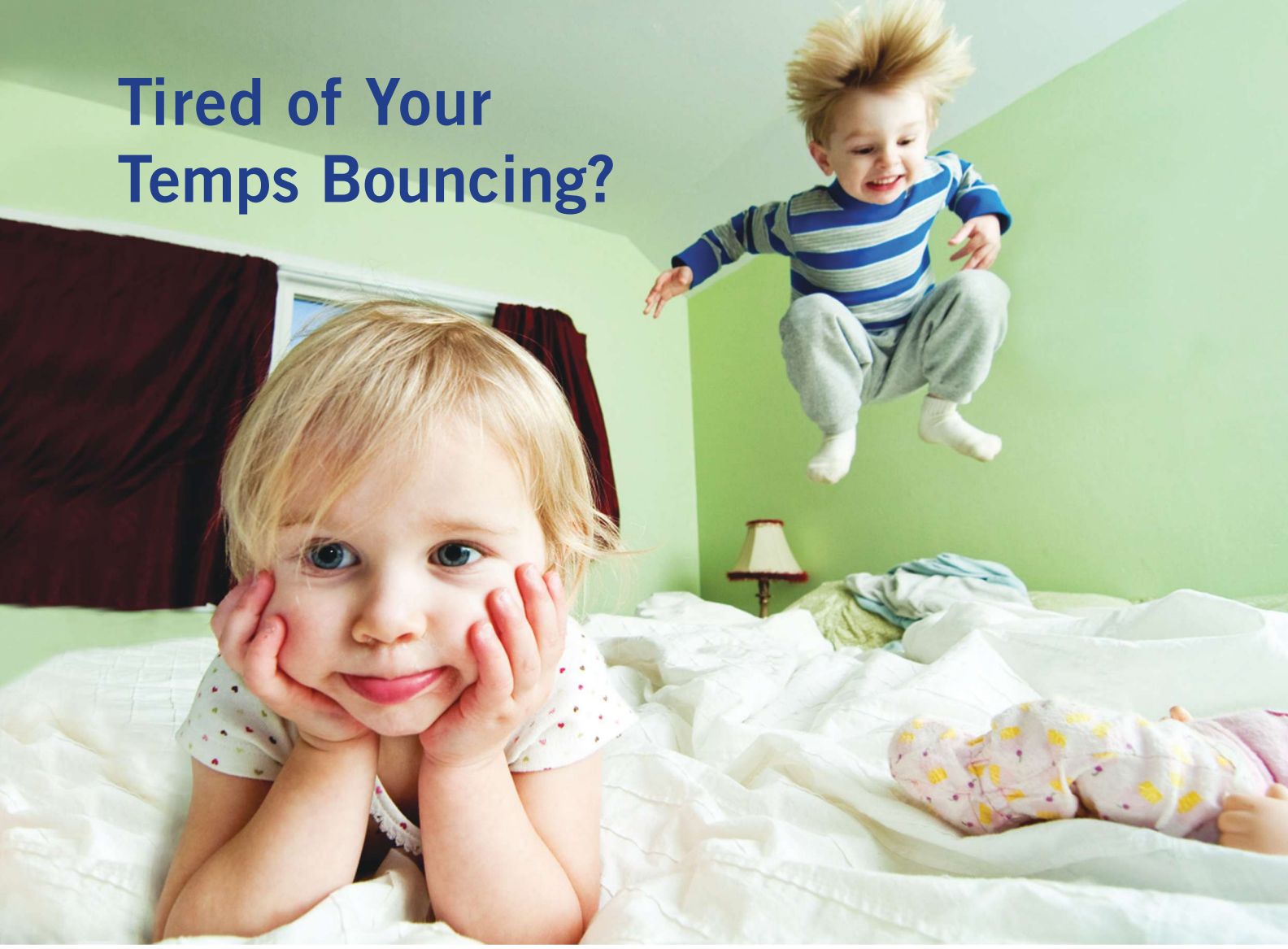
Roix has nothing but positive things to say about her clinical trial experience. In fact, Roix even gave testimony before the FDA in September 2014, asking them to approve two new IPF drugs. "In October [2014], those two drugs were approved," she states. This created a dilemma for IPF clinical trials. "I believe people are dropping out of IPF trials because now that there are two new FDA-approved drugs, patients would rather take a chance on the known, an approved drug, vs. the unknown, a clinical trial," she relates. Roix believes the pharmaceutical industry needs to push for selecting people to participate in a trial who will want to see it through to the end. "Yale did ask me whether I wanted to stop the trial and take one of the two newly approved drugs or continue the FibroGen trial," she says. "I chose to stay the course, even before agreeing to testify before the FDA. The trial gave me hope, and I hope to contribute to finding a cure." As for what advice she has for how to make trials better, Roix says, "This is the day of social media, and we all talk to each other." Through social media, she learned there really isn't any consistency among the FibroGen trial sites. "Some centers provide free parking," she says. "Some trial participants share that they get monetary compensation, like $100, just for driving to their center." Roix has to pay $15 for parking for every visit. When you think about it, this means she could have spent 40 hours, not including drive time, and $240 just to receive a placebo. Though she says she knew this going in, for others to learn that not everyone is being treated equally can be very disenfranchising. Another thing Roix would change is for more nonresearch doctors to become bigger advocates for clinical trials. It wasn't until she arrived at Yale that the possibility of participating in a clinical trial was ever suggested. "I had come from where doctors were telling me absolutely nothing other than 'Take this pill, and I'll take care of you,' to Yale, where the clinicians, doctors, and nurses are so willing to tell you every single step of the way what's going on."

One final clinical trial improvement suggestion from Roix is to develop collaborative research agreements among medical institutions. For example, on a high-traffic day, Yale is about an hour drive for her, while UCONN Medical Center is only a mere 10 minutes away. "I know others have to travel 6 hours to get their infusion every three weeks, so I consider myself lucky," she laughs. "But it would be convenient to have my trial at some place closer, or if possible, at home."

"It would be convenient to have my trial at some place closer, or if possible, at home."

LAURA ROIX

Tired of Your Temps Bouncing?



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A BEHIND-THE-SCENES LOOK AT THE PATIENT CLINICAL TRIAL EXPERIENCE | By R. Wright

CONTRACEPTION AND LACK OF COMPASSION CAN MAKE ONE CRAZY

"My baby may wake up, I'm just warning you, but right now he's sleeping so it should be fine," says Victoria Fenty. This is how the conversation began with the 33-year-old Minnesotan. I soon learn she is the mother of four boys, the most recent being just four weeks old. "I tried twice to have my tubes tied when I had my C-sections, but they were unsuccessful due to large amounts of scar tissue," she shares. "So my last doctor recommended Essure [permanent birth control], which blocks your fallopian tubes." On the day of her procedure, Fenty was asked if she would be interested in helping gather some information. Apparently, the Mayo Clinic in Rochester, MN, was conducting some sort of study. "Instead of having the X-ray to verify proper Essure placement, which I had been told was pretty painful, they were verifying proper placement by ultrasound," she states. In addition to the benefit of having a less-painful placement verification procedure, neither she nor her insurance would be charged for the product, which at the time was about $1,500. Further, she would be given a flat $45 payment for the required follow-up visits at six weeks, three months, one year, and five years.

Fenty began participating in the study in March 2012 — three years *before* she had her recent baby! "Essure's still in me. They are still following me. I reported the pregnancy, but we haven't discussed anything further. I have to see a specialist about having a hysterectomy to have it removed." According to Fenty, because she agreed to participate in the study, her paperwork specifies that if the product fails, resulting in a pregnancy, she would receive $800. "I'm still waiting on the $800," she says. But having an unintended pregnancy wasn't the only problem she experienced with the 12+ year FDA-approved product. For starters, after it was put in, she says she had continuous bleeding for about eight weeks. "I went to see my doctor, and he just said it could be a side effect of my body adjusting to it." At 12 weeks, Fenty says her doctor put her on some hormonal medicine to try to get her bleeding regulated. "The medicine worked while I was taking it, but as soon as I stopped, the bleeding came back," she recalls. "I had bloating that made me look like I was four-months pregnant, but I didn't have any pain." While Fenty felt frustrated by the bleeding and bloating, it was the reaction of her healthcare provider that bothered her the most. "You listen to your doctor, you know, you trust them, and then they're telling you your problems aren't coming from Essure," she says. "Well, what is it from? Can we find out? My body's not right. Honestly, there were never any answers. I just started dealing with it [bleeding] for 20 days a month. You really start to think you are going crazy." Fenty says when the doctor finally said, "You're just going to have to deal with it," she decided to find another doctor.

"Explain things, instead of just handing us a packet that means nothing to the average person."

VICTORIA FENTY

Was Fenty a good candidate for the product in the first place? For starters, she has idiopathic thrombocytopenic purpura (ITP), an autoimmune blood platelet disorder that can lead to excessive bruising or bleeding. In addition, Fenty has an allergy to nickel, which she says she knew about prior to having the Essure implanted. "Nobody ever mentioned there was nickel in it," she says. "I guess when it was owned by Conceptus, it [nickel] was not listed [in the label], but it's listed as an ingredient now." Hypersensitivity to nickel is also now listed as a contraindication.

You might think based on this experience Fenty would be reluctant to participate in another medical study. Actually, she recently enrolled her newborn into a circumcision study being conducted by the Mayo Clinic. "I have no problem when trials are explained so they are easy to understand," she says. Fenty shares that all of her boys have had the procedure, with the three previous circumcisions being covered by insurance. For the latest she had to pay out of pocket, because insurance is no longer covering the procedure. She receives no compensation for enrolling her newborn in the study. "It's basically just to help them [Mayo] and try to get insurance to reconsider this as a covered benefit, as the benefits seem to outweigh the risks." Her advice to anyone involved in conducting medical studies or clinical trials is to be more informative, without all the medical jargon and pieces of paper. "Explain things, instead of just handing us a packet that means nothing to the average person," she concludes.

Failed clinical trials come at a tremendous cost to pharmaceutical sponsors. While all three of the people interviewed expressed or demonstrated a willingness to participate in future medical research, you almost have to wonder why. There are a number of reasons we could list as barriers to successful clinical trial recruitment, with lack of encouragement or support from the attending physicians probably topping the list. While the biopharmaceutical industry continues down its patient-centric path, to get there probably first requires the industry to get back to its physician-centric roots. Finally, healthcare providers have become highly focused on the measurement of patient outcomes. Perhaps it is time for physicians to first "heal thyself," by increasing the compassion and attention they have for their patients. L

Sincere thanks to PatientsLikeMe and Amanda Rusmisell for connecting me to these patients. Special thanks to Dr. Jan Vesseur, Laura Roix, and Victoria Fenty for their willingness to transparently share their experiences in the hopes of further benefitting the life sciences industry and the patients it serves.

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Making Britain The "Fastest Place" For Pharma R&D Adoption

NEAL LEARNER Contributing Editor

Competition in the pharmaceutical industry isn't just about which manufacturer discovers the next blockbuster pill. National governments and entire geographical regions compete fiercely to attract pharma companies and the billions of dollars that come with their high-value investments. The United Kingdom is the latest country to try and step up its game.

The U.K. government in June unveiled details of its Accelerated Access Review (AAR) initiative, which aims to make the U.K. nothing less than, "the fastest place in the world for the design, development, and widespread adoption of medical innovations." British manufacturers naturally welcome the effort, but contend the country has a ways to go in meeting its ambitious goals, especially in the adoption of new medicines.

"New medicines can play an important role in transforming patients' health, but in the U.K., patients are not getting access to these medicines," says Alison Clough, acting CEO at the Association of the British Pharmaceutical Industry. "We lag considerably behind comparable countries when it comes to patients benefitting from new medicines."

Indeed, the uptake of innovative products launched between 2007 and 2012 was slower in Britain than in 16 other industrialized countries, according to the U.K. government's report *Life Science Competitiveness Indicators*. The U.K.'s uptake is only 11 percent of the average of other developed countries after one year, less than a third of the average after two years, and still only half the average after four years, Clough said in a statement regarding the study.

"Not only is this a disadvantage for patients in the U.K. who are not able to access the newest, most innovative medicines when they need them, but we can now see that this is a disadvantage to the country as a whole impacting our global competitiveness," she said.

The government's competitiveness report bears this out. The total value of goods and services (i.e., gross value added) generated by the pharmaceutical industry declined from a high of nearly $24 billion in 2010 to roughly $20 billion by 2013, where it remains flat. Furthermore, government spending on R&D has declined in recent years, as has the share of U.K. patients recruited to global studies. On the bright side, the report found that the number of science graduates and employees in Britain's pharmaceutical manufacturing industry is gradually rising.

AAR LAYS OUT KEY THEMES FOR REVIEW

To improve the overall picture, the AAR initiative will focus on several key themes for review. These include establishing the need, priorities, and principles for innovation; exploring new development pathways; aligning national funding models to drive innovation; and speeding up local adoption and diffusion of innovative products.

Leaders associated with the AAR say the goal is to better understand the needs and demand for innovation, which can then be translated into research followed by accelerated development of products. "We aim to translate the unique features of our science and healthcare system into meaningful benefits that will attract innovators to conduct their R&D in the U.K.," Stuart Dollow, founder of Vermilion Life Sciences and a member of the AAR expert advisory group, said in a late June posting on the government's website.

Dollow and others involved with the review aim to finish their initial work by the end of the summer and will look specifically at making reform recommendations in three areas:

- **REGULATION** – The goal will be to quickly assess safety and efficacy of innovative products by better exploiting the U.K.'s advantages as an integrated healthcare system with renowned research medicine ethics and infrastructure.

- **REIMBURSEMENT** – The AAR seeks to adapt systems of health economic assessment that reflect technological advances in genomics, precision medicine, and informatics; reduce time and risk from the traditional R&D model; and develop new models of reimbursement for innovative products (such as payment by results).

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- **UPTAKE** – The plan is to ensure that the National Health Service (NHS) can better support and drive medical innovation.

Clough says the industry has urged the British government to take a comprehensive approach to drug discovery, development, regulation pricing, value assessment, and usage. This includes better aligning recommendations of coverage made by the National Institute for Health and Care Excellence (NICE) with the approvals granted by the NHS England. "A key change needs to be the formation of a holistic research and health system, which supports both the development of research in parallel with faster patient access to modern medicines," says Clough.

LOOKING FOR EARLY APPROVALS

U.K. drug giant AstraZeneca (AZ) agrees the country could do more to speed up delivering products to British patients. An AZ spokesperson tells *Life Science Leader* that the manufacturer would like to see NICE's value-assessment framework for new pharmaceuticals better aligned with the European regulator's approach, which has sought to accelerate approvals for medicines in disease areas with limited treatment options. Unfortunately, today, the system consists of a disjointed patchwork of regulatory and value-assessment bodies, which ultimately delays access for patients.

According to AZ, the formation of a system that lets patients access newly licensed medicines that have been approved on the basis of early trial data would be extremely welcome. "This would enable U.K. patients to gain early benefit from new specialized treatments, particularly where there is unmet medical need," the spokesperson explains. "The advent of personalized healthcare and targeted treatments requires innovation in trial design and development pathways — regional regulators must be prepared for medicines of the future being developed now."

Other national oversight bodies, including the FDA and the European Medicines Agency (EMA), already are piloting initiatives in which drugs may be approved on a graduated basis as more evidence is brought to light on the safety and efficacy of the products.

"The [AAR] review should be about improving access to the latest treatments with a view to improving long-term health outcomes," AZ's spokesperson says. "The U.K. has a poor record with regards to access as demonstrated by the government's own life sciences competitiveness indicators."

U.K.'S COMPETITIVE POSITION STILL STRONG

But not everyone sees the U.K. falling behind in the race to attract pharmaceutical activity. A June report commissioned by PhRMA finds the U.K. second only to the U.S. among 16 markets on overall attractiveness for biomedical investment. The U.S., U.K., Switzerland, and Ireland, respectively, have the highest overall scores, and their biomedical environments fall into the category of "strongly competitive" relative to the other sampled economies, says the report released in late June. "All four boast excellent and effective scientific research systems, regulatory frameworks that meet the highest international standards, pricing and reimbursement systems that provide comparatively better opportunities for market access, and generally positive market conditions," it added.

PhRMA's 2015 Biopharmaceutical Investment & Competitiveness (BIC) survey noted that while the U.S. and U.K. particularly excel in the quality, scope, and effectiveness of their scientific research systems as well as clinical research capabilities, Ireland and Switzerland lead the pack in manufacturing capacity. "The U.S. and Switzerland dominate the charts in terms of providing effective intellectual property protections," the report notes. "It also is worth mentioning that, not surprisingly, these economies have reached these levels of success predominantly through the use of market-based pro-innovation policies and initiatives, including policies aimed at biomedical products."

The BIC survey examines the overall ecosystem in which biomedical innovations take place by looking at several key areas: (1) ability to leverage scientific capabilities and infrastructure; (2) state of the clinical environment, from test tube to patient; (3) quality and efficiency of biomedical manufacturing and logistics operations; (4) soundness and effectiveness of the biomedical regulatory framework; (5) healthcare financing; and (6) overall market and business conditions.

The U.S.'s score on this BIC survey was 86.88, the U.K.'s was 82.60, Switzerland's was 82.56 and Ireland's was 82.17. By contrast, China had a score of 57.62 and Brazil had a score of 56.57. The top four performers all experience challenges in certain areas that do not permit their overall scores to rise above 90 percent of the total score possible, the report noted.

In the U.S., the hurdles include a public pricing and reimbursement system for Medicare and Medicaid that is fragmented and sometimes difficult to navigate effectively. In the three other top countries, pharma executives cited fairly stringent price controls on both public and private drugs among the challenges. Governments in these countries, at times, are missing the link between investment, research, and market access in a timely manner and at a fair price, according to the report. In addition, both the U.K. and Ireland experience gaps in how they translate and commercialize research into new products. Market access incentives also are undermined by heavy use of parallel importing of medicines.

Despite the challenges, local U.K. executives still view the U.K. as a top global destination for biomedical investment. Survey respondents point to a 2014 initiative that offers companies favorable taxes on income earned from intellectual property generated in the U.K. Since implementing the new tax incentive, the economy has reported a surge in biotech investment, the report said.

Leaders of the AAR also are taking an optimistic view that the U.K. can position itself to become even more welcoming for pharmaceutical investment. "With our strong science and national healthcare system, there is untapped potential for greater research involvement and global influence to be translated into improved health," says Dollow.

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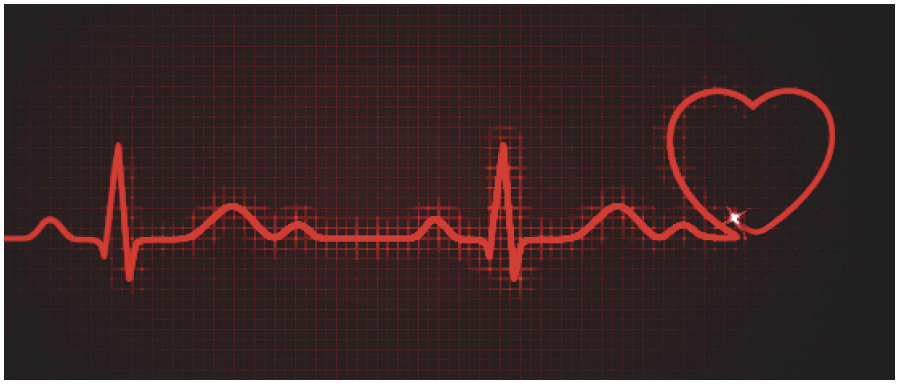
What To Know When Implementing A Compassionate Use Program

FRED OLDS Contributing Writer



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

Patients who have exhausted all current therapies to treat a serious or life-threatening disease seek hope through compassionate use of investigational drugs or what the FDA officially defines as expanded use. Patient organizations, state governments, and the FDA are all currently taking actions to expedite access to these drugs. And that easier access could conceivably mean hundreds or thousands of requests.

Ultimately, the final decision falls on the company to provide the drug. The FDA approves 99 percent of applications for expanded use. No law or agency can force a company to allow the use of a drug. To those outside the industry, the choice may seem an easy ethical and humanitarian one. But you know it's not that simple.

"The decision for approval or denial puts companies in a difficult bind," says Jason Byron, manager, medical ethics at UPMC Presbyterian Shadyside Medical Center. "Obviously everyone wants to help desperate patients, but the company has no ethical duty or obligation to provide compassionate use. The ethical duty is to provide safe and effective care. We're not sure these products are safe and effective until they go through the entire approval process."

If a company decides to provide compassionate use drugs, Byron says there is an ethical obligation to be fair in allocating the drugs. J&J's Janssen is trying to achieve that level of fairness by partnering with a third party. The company is piloting a collaboration with a committee formed by Dr. Art Caplan at NYU that includes physicians, bioethicists, and patients to review requests for compassionate use of Janssen Pharmaceuticals.

QUESTIONS TO ASK BEFORE EMBARKING ON A COMPASSIONATE USE PROGRAM

With no ethical or legal imperative to provide expanded use, the choice may come down to what's best for the "many." Does helping the "one" now delay research that will help the "many" later?

Leadership has to carefully analyze each request. Asking questions such as the following can help when making decisions related to compassionate use:

- Is there a reasonable scientific theory for use in this patient?
- Is there enough of the drug to supply patients outside clinical trials?
- Can the company afford distributing an expensive preapproved drug?
- How close is the company to submission?
- What are the liability risks?
- How will the company end the program?
- If a request is denied, will a social media campaign damage a company's reputation and result in a public or investor relations disaster?
- If approved, will clinical trials be delayed by adverse events, causing the FDA to require additional research?

WILL OUR FINAL APPROVAL BE DELAYED?

Richard Mosciki, M.D., FDA deputy director for science reporting, recognizes that research companies have a real concern about the possibility that adverse events occurring with expanded use may delay final approval. He says, "It's [a delay in the FDA's approval] a rare event, but not zero." Mosciki said that searching the memories of his colleagues spanning nearly four decades of drug approvals and reviews, very few situations came to mind. In fact, he said in a recent review of 5,000 expanded-access INDs (investi-

gational new drugs), only two instances of a drug being delayed were identified.

"Our reviewers are very aware that these populations are at a higher risk for adverse events," says Mosciki. "They recognize that the disease itself often causes what appear to be adverse events. The circumstances surrounding an adverse event in expanded use are different from those in the carefully selected population of a clinical trial. Reviewers understand this, and they make that distinction."

LIABILITY IS ANOTHER CONCERN

We all know that patient outcomes affect stock prices and, ultimately, a company's valuation. Furthermore, considering there are unbudgeted costs (e.g., monitoring, personnel, time) involved with running a compassionate use program, investors may question leadership's decision to offer it. That's why Dan Brettler, life science practice leader at Conner Strong and Buckelew (an insurance, risk management, and employee benefits brokerage and consulting firm), says liability is another concern companies should have regarding compassionate use programs. "If a company develops a strategy against offering compassionate use, it will have to be prepared to defend that position against negative social media publicity," says Brettler. "An investor may sue not only for what they think is a bad decision, but for actions management took that harm the reputation of the company. It only takes a reasonable dip in the value of stock to draw plaintiff firms out of the woodwork on just about any low-hanging litigation issue."

Insuring against these risks can be very difficult, since many are new and not well-defined. "You deal with investor loss by protecting directors and officers with liability insurance," says Brettler. "But there are only certain risks you can transfer to insurance." Leadership has to review policies for each known or potential risk to determine if it is covered. Not all policies cover compassionate use.

DEVELOP A PROACTIVE COMMUNICATION PLAN

"Reputation has a financial value," says Hugh Braithwaite, CEO of Braithwaite Communications, a marketing and PR firm that has worked with various pharma and life sciences companies. "As much as 50 percent of a company's value can be tied to its reputation." Braithwaite suggests establishing an SOP in advance to prepare for unexpected situations. The first step is to lower the threshold for what a company defines as a crisis. Braithwaite says any challenge to a company's reputation should be considered a potential crisis. Then define the foundation, the guiding principle, by which leadership will make decisions so emotions won't cloud considerations in the heat of the moment.

Take a cross-functional approach to assess risk. Have each company function predict risks associated with potential threats to the company, e.g., a social media campaign arising out of a drug denial. Using the established guiding principle, test responses to each of those risks, and ask, "Would we do this if we cared about our reputation?"

There are three steps to crisis management:

1. Validate the concern.
2. Show action.
3. Control the narrative.

Instinctively, validating the concern seems difficult because leadership wants to support its position. Even if a company is clinically, legally, and scientifically correct, the public may still disagree. "If 1,000 people online think it's a problem, then it's a problem," says Braithwaite. Restraint in responding is critical. He warns it's very easy for a company to make a public statement showing sincere compassion and understanding and, in the same sentence, invalidate its concern with the word "but." Do not follow a statement of compassion with a defense of the company position. Just outline the actions the company will take.

"You have to do something, so do anything that says you care," says Brathwaite. If the company decides not to provide expanded use, it may be able to set up additional research or find alternative studies for which the patient may qualify. Leadership also can make public appearances with patients and patient groups.

Controlling the narrative is the most difficult of the tactics. "Consumers can deploy faster than a company by a factor of 10 times," says Braithwaite. Consumers have the same communication resources as industry and can use them to affect their community actions within hours or a day. Companies are slowed by board actions, approvals, and their sheer size.

This emphasizes the need for preplanning. "You can control the narrative by preemptive action," says Braithwaite. "For instance, many of the statements and comments you'll need in a crisis can be written in advance." It's good practice to become involved with patient organizations that may benefit from your products. The company can provide information and assistance to the group, stay abreast of issues, and possibly control conversation contemporaneously. Braithwaite says, "If you're involved with the community, you'll see trends as they develop and be able to head off problems before they occur."

A COMPANY PLAN FOR HUMANITARIAN AND BUSINESS CONSIDERATIONS

When developing a compassionate use plan for its investigational drug SAGE-547, Sage Therapeutics reviewed its resources and analyzed future needs. The plan is a response to the humanitarian requests of patients and a way to develop future clinical research sites.

SAGE-547 treats the orphan disease status epilepticus, which affects about 150,000 patients each year. Patients suffer unremitting seizures and are placed in ICU in a medically induced coma. Mortality and morbidity are 66 percent.

Sage received individual expanded-use requests early in the research phase. Leadership assessed it had sufficient resources and began training ICU staffs to run the 547 trial protocol. As more patient requests were received, Sage united existing protocols into one expanded-use protocol, which allowed new patients faster entry. This presented an opportunity for the company. Because Sage trained personnel in those ICUs to use the clinical trial protocol, it expects some of those ICUs to join the Phase 3 trial as clinical test sites. L

Investigating The Myths About Opening A Subsidiary In Japan

ADAM KENNEDY

I was perplexed.

Here I was speaking with several biotech executives at the BIO Asia International conference in Tokyo, and *none* of them had any plans to establish a presence in Japan.

Why not, I wondered. After all, Japan is home to approximately 127 million rapidly aging people. It is the second-largest pharmaceuticals market and the most prosperous country in the region (per head). It has a national health insurance system and some of the best doctors and specialists in the world. There's no doubt that sufficient patients exist in Japan for a subsidiary to be not just viable, but also profitable.

Yet, for many pharma companies, Japan remains an enigma, a great unknown, where products take forever to get approved; pricing is, at best, opaque; the sales channels are impossible to comprehend; English is barely spoken; and it costs a fortune to do anything. "You're probably better off out-licensing to a local partner. Right?" commented one of those execs at the BIO conference.

Perhaps I'm biased; I have been working in this market since 2002. I know what the country has to offer, and I know there are a significant number of English-speaking Japanese professionals here.

So I decided to investigate some of the common objections (i.e., myths) biopharma companies have regarding setting up and doing business in Japan. To help me, I interviewed two non-Japanese businessmen — Steve Engen and Robert Claar — who have both successfully helped companies establish locations in Japan. Engen runs his own consultancy, Renegen LLC, and has previously set up and run three pharmaceutical companies in Japan (two subsidiaries and one local company). He's also a Japan advisor to Locust Walk Partners. Claar is the founder and CEO of Vorpal Technologies, a firm that helps companies develop their products in Japan and build a local footprint before making a decision about how to commercialize. For personnel issues, I draw on my own experiences and those of my colleagues at Morunda KK, a Tokyo-based executive search firm focusing on the pharmaceutical market in Japan and Asia.

First, let's look at the drug approval process, perceived as prohibitively slow. Many firms would be surprised by the Japanese government's recent reviews of the Pharmaceutical Affairs Law as well as its heavy investments in streamlining processes, especially when it comes to innovation and unmet needs. As Engen points out, "The regulatory environment in Japan has improved significantly over the past few years. It is entirely feasible to carry out regulatory consultations and clinical studies in Japan without a partner. For innovative products that fall under the new Regenerative Medicine law, it is now possible for a company to file for conditional approval in Japan with confirmed safety and a modest amount of Phase 2 data. The new Sakigake system also offers the opportunity for expedited review timelines." This moves Japan ahead of many Western countries when it comes to the environment for innovation. Claar says, "Approval times are continuing to improve in Japan, and the PMDA [Pharmaceutical and Medical Devices Agency] is transparent and predictable regarding clinical design." Additionally, the government added more reviewers to the PMDA, helping to reduce review times.

So we can conclude that the regulatory environment here is not the problem it once was. Coupled with this, support from the relevant KOL community is likely to be very high, because "foreigners are welcomed with open arms, and in fact, it can be easier for foreign firms, compared with local companies, to develop meaningful relationships with KOLs, who will want to work with you," Claar says.

Turning to market access and pricing, it's well-known that the Japanese government reviews long-listed prices downward every two years. However, according to Claar, "You can get premium pricing in Japan for innovative products, often based on the undiscounted list price in overseas markets, which is a

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significant incentive." He adds that there could be lower hurdles to market access for innovative drugs in Japan as compared with some overseas markets. "Once the senior clinician is keen to prescribe the drug, having it added to the formulary can be relatively straightforward," he explains.

HIRING LOCAL MANAGEMENT HAS ITS ADVANTAGES

There's no doubt it can be expensive to set up in Japan. But it can be done in steps, allowing you to build your presence in line with your launch plans. Claar suggests working with a trusted local partner that acts as an in-country caretaker that will develop your products and act as your market authorization holder (MAH — you will not be able to sell your products in Japan without an MAH) here until an agreed-upon stage when you might opt to buy your license back (at a prearranged price, rather than being at the mercy of your local licensee or CRO). The actual structure of this could be tailored around each company's needs, but it might enable you to concentrate your efforts on building your commercial and medical teams' activities. Having this kind of partnership also can help you select and manage a local CRO, offering you peace of mind.

Organizations such as JETRO (Japan External Trade Organization) offer a lot of practical help to companies establishing an office here, including use of an office for three months as you set up.

Engen notes that costs of hiring local leadership are very comparable to other markets. "If you have the right people with the right mindset, you can succeed in Japan," he says. "The challenge is whether you can manage cross-culturally in this market." It's well documented that English-speaking talent in Japan is comparatively limited, and competition for it is fierce. But a cursory glance at the leadership of the vast majority of successfully run multinational corporations in any industry reveals the presence of bilingual Japanese executives. They do exist. In fact, for a Japanese candidate to be promoted from manager to director with a foreign-capitalized company, they have to be able to communicate with global colleagues.

In my opinion, the cultural divide in Japan is often overstated and sometimes can be used as an excuse to cover other problems companies entering this market may have. Just as there are companies that have made wrong leadership decisions and subsequently found life difficult here, there are numerous examples of firms that have been able to bridge this cultural gap to be successful. The biggest danger is that you choose someone who does not fully engage with your headquarters and allows your subsidiary to drift. If a company is considering setting up an operation in Japan, one option would be to send someone over from HQ to set up and run the business here for, say, three to five years. Although likely having no experience in Japan, this individual would understand the corporate culture and communicate with HQ during the critical initial years. However, in this scenario, it has been our experience that hiring a local executive in a COO-type role can be beneficial. They would work directly under the local president, giving the company both Japanese and HQ acumen and setting up a potential succession plan once the corporate HQ staff departs Japan. Engen says another option would be to hire a candidate who has a successful track record of establishing and operating pharmaceutical companies in Japan. Of course, there are relatively few of these individuals in Japan, though.

IS OUT-LICENSING THE ANSWER?

Engen says that while establishing a Japanese subsidiary to advance the development of your pipeline should add significantly to the value of the company, you have to remember that in doing so, you could lose control over your products and strategy if not managed correctly. "Often, companies that out-license in Japan are frustrated with the information flow and transparency in their local partner relationships. Building into these agreements some ability to have a local presence, including comarketing, could make a big difference," he explains.

"There is no substitute for having your own feet on the ground in Japan," Claar adds, echoing a feeling of helplessness that many companies share when they sign away their prized assets only to see disappointing returns. Also remember that the pipelines of potential suitors here will likely be far from robust, so it is in their own interests to make Japan seem as impregnable and unique in order to dissuade you from selling your own products here under your own strategy.

So, how *does* a company decide to expand into Japan? Engen feels this should be a board-level decision rather than one made only by senior management. Accordingly, it is important to understand the priorities and interests of the board with respect to Japan. Being successful in your core markets is no guarantee of success here, and there is a danger that Japan may prove to be a distraction for your senior management — an expensive distraction. Indeed, there are a good number of companies in many industries (that I certainly could not name here, but they will know who they are) whose Japanese subsidiaries are or were considered failures.

Japan may not work for every company, despite the potential rewards. But many U.S. biotech companies (e.g., Celgene, Biogen, Shire, Gilead) have successfully started Japan operations, and some smaller companies (e.g., Aegerion, Synageva, Biomarin, NPS) have done so, too, Engen adds. L

Adam Kennedy is a director with Morunda KK, an executive search firm focusing on the pharmaceutical sector in Japan and Asia. Originally from the U.K., Adam has been active in this market since 2002, after several years in finance and operational management in the National Health Service.

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Quality In The Biologics Discovery And Development Continuum

TIM MORAN

Tim Moran is product manager, life science research, at Dassault Systèmes BIOVIA. Tim's early research in the industry focused on immunomodulation and imaging to study effects on T-cell lymphocyte homing. He has held several product management roles in image informatics.

With biologics filling the pipelines of life sciences companies more than ever, the industry needs to rethink its view toward quality. Once primarily considered a focus in downstream drug development and manufacturing, the issue of quality now demands attention in upstream discovery research as well. In fact, the line between discovery and development in biologics looks more like the intersection of a Venn diagram than a line at all, with discovery and development sharing space in the drug development quality continuum.

WHAT IS DRIVING THE NEED FOR QUALITY EARLIER IN THE PROCESS?

The need to focus on quality early on in biologics results, in part, simply from the complexity of biologics, as well as the increased regulatory scrutiny required when working with living organisms as source materials from early research through production of biologics. Added complexity in the development and manufacturing processes can often be mitigated by instituting quality processes in the early stages of biologics discovery. The concept of Quality by Design (QbD), postulating that quality cannot be inspected into products, but rather is created by processes, has become an increasing focus for companies committed to designing and developing successful therapeutic candidates.

The cost of adhering to quality processes in late-stage development can often be drastically reduced by adhering to and understanding quality methods early in the discovery process and then adhering to those processes in development and manufacturing. Done well, QbD works like a lever, enhancing good scientific practices and encouraging scientists to take the long view and not cut quality corners on the road to releasing an approved therapeutic product; as such, QbD can confer significant competitive advantages.

ASPECTS OF REGULATORY GUIDELINES

The industry is facing increased regulatory requirements for documenting the use of predictive analytics on vast data sets, combining knowledge from early-stage research, historical data from the public domain, preclinical experimentation, clinical trials data, and even postmarket analysis data. Many of the regulations imposed during biologics development and manufacturing to produce reports on processes such as biophysical characterization, post-translational modifications, aggregation propensity, and other developability properties can be tested early in the product development life cycle. Additionally, regulatory agencies require comparability studies from preclinical to clinical product development samples.

Preventing aggregation in solution provides an interesting example of how the research stage can contribute to QbD in biologic entity development. Two challenges arise: first, how to get the biologic to a therapeutic concentration without unwanted aggregation and, second, how to get the biologic through scale-up without aggregating. An organization obviously wants to avoid aggregation in a phase separation column that costs over $1 million to pack. Better understanding of the design space through the use of *in silico* tools enables scientists to modify the biologic to reduce aggregation prior to scaled-up production. The cost and time-to-market benefits can be immense.

COMPLEXITY IN LIVING SYSTEMS AS A DRIVER FOR QUALITY IN RESEARCH

Biologics are often produced in cell lines. Cells themselves are complex entities. Even heterogeneous populations are susceptible to such things as somatic mutations and environmental stimulation, leading to changes in such things as methylation states and subsequently expression. Cell-line developers in discovery now may have responsibility to ensure that they have the necessary traceability, documentation, and security in place to support handoff to process development. For example, a cell-line developer in discovery may need to prove to the FDA that the biologic came from a single (mono) clonal cell line. Life sciences research companies have been submitting plate-based images as proof of monoclonality along the discovery and development continuum. The development of standard operating procedures around functional assays (for example, studies and cell-based assays) can often be optimized in early research, saving both time and money in later stages of development.

It is in the industry's best interest to focus on QbD early in discovery research. Applying quality results from early research and preclinical studies in safety and efficacy can not only enhance the predictive models on developability but also reduce variability, produce more effective therapeutics, and reduce late-stage costs and failures. Quality, after all, is a business as well as a technical imperative.

How Serialization Can Help Your Pharma Brand

YVONNE SARGENT

Yvonne Sargent is a packaging and serialization consultant at ESP (Enterprise System Partners), a global consulting and project engineering company that has supported manufacturing IT solutions for the life sciences industry since 2003. She has worked for leading global companies in areas such as project management, process development, packaging validation, operations management, serialization, and lean Six Sigma.

By now you probably know that serialization is your best option for combatting counterfeit pharmaceuticals. Unfortunately, you probably also understand that developing and implementing a serialization plan is no simple task. Your packaging, warehousing, and supply chain processes all will be altered, which involves a lot of change management for any organization. The primary goal, of course, is safe and secure drugs for patients, and yes, regulatory compliance is part of the equation. But many people underestimate the additional positive effect serialization can have on a company's brand.

DISCOVER PACKAGING ERRORS EARLY

Serialization can significantly reduce the risk of product recalls by making it more likely that you will uncover a packaging/printing error while the product is still under your control. For example, packaging errors are typically related to component artwork, the printing of variable data (e.g., lot number, expiry date, manufacturing dates), and component quality (carton and ink), which affect the legibility of the code as it moves through the supply chain.

Typically when introducing a serialization program, there will be an increased focus on in-process checks at a packaging level, ensuring that defect levels are reduced. When validating the printing and vision equipment associated with serialization, you likely will be faced with challenges related to print quality, readability/legibility, testing of 2D code quality, and similarity testing — where the vision system is challenged to detect between similar numbers and letters (e.g., 6 and 8; 8 and 9; a, c, and o; f and t).

If a product *does* have to be recalled, with a serialized system in place, you will be able to respond more quickly. Doing so not only helps protect the patient, it demonstrates to regulators the control you have over your supply chain and quality management system procedures, and ultimately it limits the damage to your company's reputation.

THE BENEFITS OF SERIALIZATION ON YOUR SUPPLY CHAIN

The following are some of the benefits serialization offers to your supply chain:

- Improved visibility of products as they move through the supply chain will consequently reduce product shrinkages and losses.
- Your expiration date-management system will become more efficient. Regular stock controls such as cycle counts can be performed with greater efficiency by using system-generated data. That data can be reviewed with greater ease and at a frequency that suits the business, thus minimizing stock write-offs. (Traditionally this may have been performed by manually counting stock.)
- While serialization will not provide companies with any specific sales data, as the product moves through the supply chain and touches various points (e.g., distributors, 3PLs, warehouses, pharmacies), greater visibility of product movements will become apparent, which enables smarter sales forecasting.
- Serialization will greatly reduce — and maybe even eliminate — product diversion incidents whereby genuine product is fraudulently diverted to be sold in a different market than it was intended.
- You will experience improved inventory management of both finished goods and consumables (e.g., inks, wrapping materials, cardboard, pallets).

PLAN AHEAD WITH YOUR TEAM

There are several teams that should be considered part of any serialization plan. At a site and packaging level, personnel from supply chain, production, automation, engineering, IT, quality, and regulatory affairs will all be impacted by the introduction of serialization. Before implementing your serialization strategy, talk with the employees in these departments, and seek to understand their perspectives on how their jobs may be affected or what suggestions they may have for process improvements. And keep that dialogue going throughout the implementation process.

The greater automation and data management associated with serialization equipment allows companies to use this information to save time on line changeovers as opposed to having to perform manual counts. Many companies have utilized this additional focus on their packaging function to implement 5S and other lean tools, as it provides an opportunity to take a holistic view of your production area and implement improvements. L

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The Light Touch: Are You A Boss Or A Leader

BOB GARNER

Willie Shoemaker is probably one of the best-known jockeys who ever lived. He once said, "I keep the lightest touch on the horse's reins. The horse never knows I'm there, until he needs me."

The person who is a leader also needs that "light touch." A leader must remember that their role is to create a vision and then surround themselves with the best people who can accomplish that goal. The leader can show what needs to be done, but then the leader must step aside and let people do their jobs.

However, often that is not the approach of many leaders who feel that they have to be a part of every decision — no matter how trivial. By constantly micromanaging every decision, a leader transforms into a "boss" revealing not only a lack of trust for employees, but also, possibly, some control issues.

LET THE PEOPLE *YOU* HIRED DO THEIR JOBS

Employees were hired — and still have a job — because they are experts at what they do. They have skills and talents that need to be unleashed and nourished, not bridled and suffocated. A leader gets out of the way and lets the experts do their jobs, while a boss feels the need to control. If every decision needs to have the "green light" from the boss, be prepared for major bottlenecks in productivity and stifled creativity, as well as decreased morale, teamwork, and communication.

Micromanaging is just one issue a boss does that a leader doesn't. A few more were famously provided by the controversial, yet one-time successful retail magnate Harry Selfridge. He stated, "The boss drives people; the leader coaches them. The boss depends on authority; the leader on goodwill. The boss inspires fear; the leader inspires enthusiasm. The boss says, 'I'; the leader says, 'We.' The boss fixes the blame for the breakdown; the leader fixes the breakdown. The boss says, 'Go'; the leader says, 'Let's go!'"

Bob Garner is a successful entrepreneur, author, and funny motivational speaker with clients worldwide. Read his amazing story at www.bobgarneronline.com.

> *"A leader gets out of the way and lets the experts do their jobs."*

CREATE AN ENVIRONMENT WHERE MISTAKES AREN'T ALWAYS CONSIDERED BAD

With that said, a possible downside to being a leader versus a boss is that, with more freedom and latitude to "do their jobs," there is the possibility that employees may make more mistakes than those who have less autonomy. But, as the "Wizard of Westwood," the late UCLA coach John Wooden once said, "If you're not making mistakes, then you're not doing anything. I'm positive that a doer makes mistakes."

And that is what any leader really wants — a team of doers. And doers do when they are led by a leader and not a boss. Doers do when they are led by a leader who believes in them and encourages them. Doers do when they are led by a leader who, just like Willie, keeps a light touch on the reins and lets employees know they are always there ... if needed. L

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