Life Science Leader
Connect. Collaborate. Contribute.
SEPTEMBER 2016

Life Science Leader

Connect. Collaborate. Contribute.

SEPTEMBER 2016

Where GSK Expects To Grow

Top GSK executives such as **Luc Debruyne**, president of GSK Vaccines (pictured), outline the company's new vaccine and oncology aspirations. **p. 20**

Bringing together the best of ONE2ONE™ Pfizer CENTRESOURCE

Pfizer CentreOne

Contract Manufacturing

When it's **YOUR** compound, every step matters.

www.pfizercentreone.com

API | DRUG PRODUCT

PROVEN PHARMACEUTICAL EXPERTISE.
ADVANCED MANUFACTURING TECHNOLOGY.

Bringing a drug candidate to commercial launch is complex, demanding proven proficiency and the most-advanced technology. We support our pharmaceutical specialists with manufacturing technology from innovators in life sciences equipment. Korsch XL 400 MFP rotary tablet press brings maximum efficiency to our single and multi-layer tableting. Respected names like Glatt bring innovation to our drying, granulation and coating.

RPS provides like-for-like technology transfer for process improvement and is an ideal partner for small and medium manufacturing lots.

You improve patient outcomes. We improve the process that gets you there.

ROPACK 40 YEARS 1976-2016

PHARMA SOLUTIONS
for solid oral dosage

From Early-Stage Formulation to Market

ropack.com

Francois Chouinard, Ph. D.
francois.chouinard@ropack.com • (514) 235-9661

CONTENTS

Welcome to

Life Science Leader

SEPTEMBER 2016 VOL. 8 NO. 9

@LifeSciLeader1 linkedin.com/in/robertfwright facebook.com/LifeScienceLeader WWW.LIFESCIENCELEADER.COM

20 Cover Story: GSK

Top GSK executives such as Luc Debruyne, president of GSK Vaccines (pictured), talk about the company's vaccine and oncology aspirations.

Features:

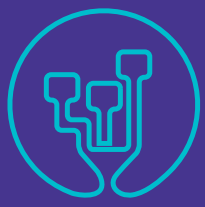
LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 8, No. 9 is published monthly by Jameson Publishing, Inc. at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5580. Periodical postage paid at Erie, PA 16510 and additional mailing offices. **SUBSCRIPTION RATES** For U.S. based subscribers, $295 for one year. If your mailing address is outside the U.S. the subscription price is $445 for one year. **POSTMASTER:** Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. **PUBLICATIONS AGREEMENT:** No. 40722524 c/o AIM, 7289 Torbram Road, Mississauga, ON L4T 1G8.

Making tomorrow HEALTHIER together.

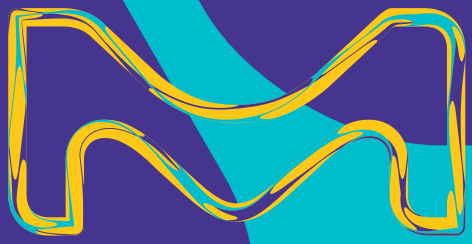
EMD Millipore + Sigma-Aldrich have come together to tackle life science's toughest challenges in collaboration with the global scientific community.

GLOBAL
1 global force across 66 countries

EXPERTISE
A wealth of experience in solving the toughest challenges



COMPLETE
Enhanced tools, resources, and customer service



Learn more at **milliporesigma.com**

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada

MilliporeSigma

Where Will The Next Biopharma Breakthrough Come From?

ROB WRIGHT Chief Editor

Ever heard of the company Galvani Bioelectronics? The name probably sounds familiar because the company was recently the subject of nearly every news media outlet, including the *Wall Street Journal*. Even more impressive is that while Galvani Bioelectronics was dominating headlines, it was doing so despite (as of this writing) it not owning a website and having only one employee and board member. How is this possible? Simple. Galvani Bioelectronics is the outcome of GSK and Google parent, Alphabet, teaming up to develop bioelectronics medicines. Kris Famm, former head of bioelectronics research at GSK, will serve as president of this new $700 million venture, while Andrew Conrad, CEO of Verily Life Sciences (formerly Google Life Sciences), will sit on its board. (Sorry Boston, despite your city being the current bastion for biopharma R&D, for the time being at least, Galvani will be based at GSK's research center in Stevenage in the U.K. So much for Brexit being biopharma's and GSK's downfall!)

To my understanding, Galvani isn't planning on taking the same approach as Otsuka (i.e., submitted the first digital medicine new drug application to the FDA in the form of an Abilify tablet being outfitted with a Proteus ingestible sensor), but instead intends to develop treatments that use miniature implanted electronic devices to modify how electrical impulses are transmitted around the human nervous system. I often have argued that for biopharmaceutical companies to go beyond being just cutting edge (see page 20 of our August 2016 issue), they need to start looking for breakthroughs of the nontraditional biopharma variety (i.e., therapeutics not based purely on drugs). Here we see a Big Pharma doing just that. However, is what GSK is doing really all that new? After all, there have been other biopharmas that have partnered with high-tech giants (e.g., Novartis and Google, Teva and IBM Watson). Further, it was over four years ago that I wrote about *GSK's Seekers of Disruptive Innovation* and described how John Baldoni (SVP of platform technology and science at GSK) came up with the idea generation team (i.e., The Seekers) to not only create tipping points, but craft them sooner.

You may be wondering: Why all this talk about GSK? Even in this issue there are three separate GSK articles. What gives?

It all started when I was making my plans for this year's BIO convention in San Francisco. One of my goals while attending was to interview as many big biopharma executives as possible, and GSK just happened to be very accommodating. But what made it a real win-win was getting the opportunity to explore, from a very high level, the details behind GSK's mega-deal with Novartis that saw $20 billion worth of assets swapped. In this issue's three-part series you will:

- learn why GSK was willing to spend $4 billion on acquiring the Novartis vaccines business
- understand that GSK's $16 billion sale of marketed oncology assets did not signify its "Brexit" from cancer drug development
- read a great story about the creation of reverse vaccinology and subsequent development of the first Meningitis B vaccines.

While it remains to be seen if what GSK and Verily have planned will eventually bear fruit, I applaud their willingness to push the boundaries of conventional thinking in seeking biopharma's next breakthroughs. L

Life Science Leader
SEPTEMBER 2016 VOL. 8 NO. 9

LIFE SCIENCE LEADER
5340 Fryling Rd., Suite 300 / Erie, PA 16510-4672

Telephone: 814 897 7700 / Fax: 814 899 4648

WWW.LIFESCIENCELEADER.COM

SVP OF PUBLISHING/PRODUCT DEVELOPMENT
Jon Howland / Ext. 203
jon.howland@lifescienceconnect.com

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

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

EXECUTIVE EDITOR
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

EDITORS
Louis Garguilo
louis.garguilo@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Anna Rose Welch
anna.welch@lifescienceconnect.com

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

DIRECTORS OF STRATEGIC PARTNERSHIPS
Tim Bretz / 724-940-7555 / Ext. 123
tim.bretz@lifescienceconnect.com

Cory Coleman / Ext. 108
cory.coleman@lifescienceconnect.com

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

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

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

PUBLISHER/BIOPHARM & LAB
Shannon Primavere / Ext. 279
shannon.primavere@lifescienceconnect.com

GROUP PUBLISHER/OUTSOURCING
Ray Sherman / Ext. 335
ray.sherman@lifescienceconnect.com

BUSINESS DEVELOPMENT MANAGER
Mike Barbalaci / Ext. 218
mike.barbalaci@lifescienceconnect.com

SR. ACCOUNT EXECUTIVE
Scott Moren / Ext. 118
scott.moren@lifescienceconnect.com

DIRECTOR OF DATA ANALYTICS
Kevin Morey
kevin.morey@lifescienceconnect.com

PRODUCT DIRECTOR
Jenell Skemp
jenell.skemp@lifescienceconnect.com

PROJECT MANAGER
Megan Rainbow
megan.rainbow@lifescienceconnect.com

PRODUCTION DIRECTOR
Lynn Netkowicz / Ext. 205
lynn.netkowicz@jamesonpublishing.com

ENVIGO

At Envigo, the positives are in more than just our name

- Leading non-clinical CRO with research model portfolio
- An extensive global footprint
- Proven scientific excellence and regulatory knowledge
- Expert data interpretation and insights
- A truly customer-centric culture
- Renowned animal welfare and enrichment

E-book download

'The true value of a non-clinical CRO'

envigo.com/truevalue

Have a response to our experts' answers? Send us an email to atb@lifescienceconnect.com.

Q What clinical trial requirements or practices could be revised to provide quick cost reductions and perhaps result in lower drug prices?

A OVERALL, I DON'T SEE REGULATORY ISSUES DRIVING DRUG PRICES, unless you are talking about fundamentally decreasing the overall cost of drug development. Drug pricing is more connected with outcomes, health economics, value-based reimbursement, and contracting power. One idea is that the FDA could provide guidance for acceptable study design (population, inclusion/exclusion, endpoints, etc.), or the agency could provide feedback earlier on specific protocols throughout the drug development process. The FDA also could encourage greater use of enriched trial designs so that if the drug is effective, it is more likely to be readily shown. Companies could also increase their use of modern/novel clinical trial selection strategies (genotype, surrogate markers, etc.) to identify specific populations with higher probability of success. Finally, companies could share study outcomes so others could apply learnings to their future trials.

MITCHELL KATZ, PH.D.
is head of medical research and drug safety operations at Purdue Pharma, L.P. He has 30 years' experience in the pharma and biotech industries.

Q List some key characteristics you look for when recruiting engineers and how to tease these out.

A ASIDE FROM ENGINEERING ABILITY, I try to assess their skills related to explaining their subject, working in a team, and negotiating corporate bureaucracy. Technical professionals need to be able to explain concepts to people with a wide range of scientific acumen. Ask a candidate to explain one of their projects, or listen to them describe a technical drawing you show them. Have the candidate speak with interviewers from various job functions. Get the candidate to provide detailed descriptions of previous work environments. Watch how they function within the context of your job application process. The candidate's reactions to your corporate processes ranging from parking to gate security to the cafeteria line may provide clues as to their ultimate fit with the organization.

MARK PETRICH, PH.D., PE
is director, component engineering at Global Sterile & Validation Center of Excellence, Merck. He serves as second vice chair of the Bio-Process Systems Alliance.

Q What are some fundamental challenges facing biopharma manufacturers?

A AT THE GLOBAL PHARMACEUTICAL MANUFACTURING LEADERSHIP FORUM IN FRANKFURT, GERMANY, a list of current biopharma industry construction projects was presented. Of the 23 projects listed, at least six will cost more than $1 billion, and five will be in excess of $2 billion. While we are asking our vendors to be prepared to deliver on an unprecedented scale, we should also be asking if we, as manufacturers, can deliver. While these construction projects might represent about $20 billion in capital expenditures, let's not forget that we'll also need to carry in excess of $100 billion in potential product inventory. Can we as an industry afford this? Are we about to invest in capacity only to find out after the fact that it was too much?

ANDREW SKIBO
is the head of Global Biologics Operations & Global Engineering at AstraZeneca/MedImmune.

Finesse

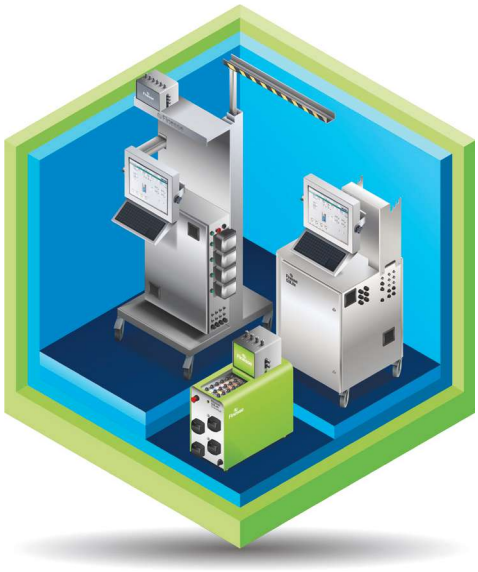
Are you really in control?

Many bio-manufacturing facilities operate a mix of old and new equipment with custom software from multiple vendors. These islands of data and automation make it nearly impossible to efficiently scale your process.

Harmonize and Optimize with a Universal Platform

Finesse SmartSystems combine our G3 Universal hardware with our TruBio® software to help you:

- Add Intelligence to older infrastructure, hence leveraging existing capital
- Migrate islands of process data and automation into a harmonized plant network
- Control leading industry bioreactors with a single automation platform



Quark Pharmaceuticals

RNA Interference, Organ by Organ

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Quark Pharmaceuticals is a pioneer in RNA (ribonucleic acid) interference (RNAi), now with its own siRNA (small interfering RNA) drugs that block targeted disease-causing genes. It has two products in Phase 3 development — QPI-1002 for delayed graft function and QPI-1007 for nonarteritic anterior ischemic optic neuropathy (NAION) — and a number of others in preclinical to Phase 2 development for a wide range of conditions.

WHAT'S AT STAKE

Skepticism is certainly appropriate at the early stages of life sciences R&D. New medical technologies historically take decades to develop. The typical pattern includes wide excitement over a simplified view of a new theoretical mechanism, followed by clinical failure and an almost simultaneous realization of the enormous biological uncertainties that undermined the original premise. Then comes years of research and engineering to deal with the uncertainties, greatly improve results, and resurrect the technology. The easiest example is monoclonal antibodies. Is RNA interference next?

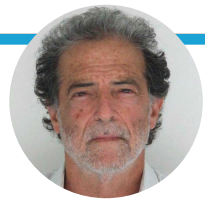
Dr. Daniel Zurr, Quark's chairman and CEO, believes it is. Not only that, he believes his heretofore dark-horse company is the one that will bring success to the field for the first time with its siRNA drugs. "We have ways to modify the siRNA so it can move into different organs in the body," Zurr says. "This is one of our key assets. We know how to deliver the siRNA to the kidney, the heart, the lung, the inner ear and eye, and even into the hair follicles — to suppress the antigen receptor involved in hair loss."

Founded in Israel more than 20 years ago, Quark invented a gene-mapping system called BiFAR, then married it later to siRNA when the technology became available in the late 1990s — changing the company's focus to drug development. BiFAR identifies disease-modifying genes as drug targets; siRNAs are the active agents that block gene expression. Those platforms, together with the company's continuing work on delivery modes, have attracted a flock of Big Pharma partners and generated numerous candidates for the company's own pipeline.

Zurr draws a contrast between Quark and its main rival, headline-winning Alnylam. "Like us, Alnylam has two products in Phase 3, but both are for liver indications because the company can only deliver its drugs to the liver. Its siRNAs are coated with liposomes or are GalNAc [galactose/N-acetylgalactosamine] conjugates, which travel immediately to the liver." Quark uses several delivery technologies, including formulations and mAbs (monoclonal antibodies), which bring the siRNAs to the right cells, where they can use their abilities as players in the innate immune system to enter the cells and interfere with disease-causing gene expression.

QPI-1002 is in a Phase 3 trial for treating delayed graft function following kidney transplant, tissue death by apoptosis that arises from the reperfusion of oxygenated blood into the transplanted organ. QPI-1002 temporarily suppresses the apoptotic p53 gene in the kidney graft. The longer the kidney stays on ice before surgery, the worse its oxygen starvation becomes and the more damaging the reperfusion injury, and donor kidneys are often discarded when delayed too long in transit or storage. Quark is investigating use of another siRNA drug, QP-CP1, for similar tissue death and scarring from reperfusion following myocardial infarction.

The complete array of indications in Quark's development pipeline is truly impressive and, I suspect, its biggest challenge — other than the inherent vagaries of invading cells and manipulating genes. At the scale of siRNAs and cellular constituents, molecules make up a quantum world where uncertainty reigns. Having passed through much of the proof-of-concept gauntlet, the company and its products' next big test will come in its Phase 3 trials, where the concept meets uncertainty at the macro scale. L



DANIEL ZURR, PH.D.
Chairman and CEO

Vital Statistics

Headquarters
Fremont, CA

Finances

About
$500M
to date.

SoftBank Investment of Japan more than 90 percent

Research Partnership Funding

Biocon
License/collaboration on QPI-1007 in India

Kunshan RiboQuark Pharmaceutical Technology
Joint venture license/collaboration on QPI-1007 in China

Other Partners

Novartis
Option license to all siRNA targeting p53 gene

Pfizer
siRNA targeting RTP801 gene

Latest Updates

March 2016:
Began two pivotal Phase 3 studies and a Phase 2 study of RNAi-based therapeutics for kidney and eye indications

June 2016:
Initiated Phase 2/3 ocular-neuroprotection study of QPI-1007 in India

July 2016:
Won key patent for QPI-1007 ocular neuroprotectant

UPM Pharmaceuticals®
Formulating Your Future™

A Commercial Facility for Today's Market

UPM Pharmaceutical's 500,000 square feet commercial facility in Bristol, Tennessee offers large-scale manufacturing capabilities for tablets, capsules and semi-solid dosage forms. The facility features state of the art equipment, including wet and dry granulation, coating, multi-pellet encapsulation and bi-layer tableting.

KEY SITE FEATURES:

- 500,000 square foot manufacturing facility
- 70,000 square feet of general warehouse storage
- 7,400 square feet of controlled substances storage
- DEA-licensed
- Comprehensive tech transfer support
- Pilot plant with scale-up capacity
- Analytical and microbial testing laboratories with dedicated suites for potent compounds

LARGE-SCALE OPERATIONS:

- Blending
- Drying
- Compressing
- Semi-Solid Processing
- Milling / Sifting
- Granulating / Coating
- Encapsulating
- Packaging

ANNUAL PRODUCTION CAPACITY:

- 3.5 billion tablets
- 700 million capsules
- 43 million packaged bottles
- 138,000 kilograms of cream / ointment
- 5 million packaged tubes / jars

To learn more, visit **www.upm-inc.com** or call **+1 423 989 8000.**

Rx Industry Vulnerable On Generic Delay In Fall

JOHN McMANUS The McManus Group

After taking nearly two months off this summer, Congress reconvenes in September with a relatively short list of health priorities to complete this fall:

- Funding to combat the spread of the Zika virus and treatment of opioid addiction
- Completion of a CURES package of modest FDA reforms and increased funding for NIH
- Possible "grandfathering in" of hospitals that were in the process of acquiring physician practices when Congress enacted the Bipartisan Budget Act last November, which capped Medicare reimbursement for services provided by those acquisitions

None of these issues materially impact the pharmaceutical industry. But there is growing chatter among congressional aides that the industry should ante up some resources to help address these yet-unresolved issues. Arrangements that delay market entry of generics appear to be the focus at this juncture.

ZIKA FUNDING

Nearly 2,000 people in the U.S. and another 6,600 in its territories, including 300 pregnant women, have tested positive for the Zika virus. Most of the cases are in Puerto Rico; in the continental U.S., they are almost all travel-associated infections. But now some mosquito-borne cases are showing up in Florida.

The Zika virus is primarily spread through mosquito transmission. It can cause microcephaly in newborns or abnormally small heads and other severe brain defects.

The Obama administration requested $1.9 billion for mosquito abatement, vaccine development acceleration, and education. The House passed a bill providing about one-third of that amount by redirecting spending from other programs. Democrats objected to the amount and argued that it should be funded through "emergency appropriations," thereby avoiding cutting other programs. The Senate bill provided substantially more funding — about $1.1 billion in all — but failed to garner enough Democrat support, in part, because they demanded money for Planned Parenthood, which was not even requested by the White House.

In August, the HHS secretary bowed to growing pressure by redirecting $81 million to Zika containment and vaccine research. Republicans argue that HHS can deploy hundreds of millions more in unobligated funds. But even this funding is seen as a stopgap measure. Let's not forget that the private sector has already committed huge resources to develop a vaccine; there are dozens of early-stage clinical programs under way.

OPIOID AGREEMENT

Despite the general gridlock in Washington, Congress achieved an important breakthrough when it enacted The Comprehensive Addiction and Recovery Act, which addresses the opioid epidemic and establishes a comprehensive approach to expand prevention, education, treatment, and recovery. The law also strengthens prescription-drug monitoring programs to help states monitor and track drug diversion and help at-risk individuals access services.

Every Democrat on the bicameral conference committee refused to sign the conference report, arguing that while it authorized funding, it failed to actually appropriate those funds. Nonetheless, in an unprecedented move, they all voted for the bill, along with most of Congress, and it was signed by the president on July 22.

The legislation authorizes $181 million a year largely for grants addressing the opioid-abuse crisis, but Republicans insist it must be funded through the appropriations process. Democrats would like a dedicated funding source. This disagreement should be worked out this fall.

We found no upside to silos, territories, handoffs, roadblocks, walls, fences, gaps or sidetracks. So we eliminated them.

First and foremost, we are focused on constantly evolving and pioneering best practices across all disciplines, streamlining procedures, removing hurdles and reducing opportunities for errors, false starts and wasted time or money. Our thinking is simple: a smoother process is a better process—and sometimes even a faster one.

Maybe that's why we have helped to develop or commercialize 81% of all Novel New Drugs approved by the FDA over the past five years. Or maybe our clients just like working with us.

inVentiv Health

inVentivHealth.com

Shortening the distance from lab to life.™

21ST CENTURY CURES PACKAGE

Last year, the House passed the 21st Century Cures bill, a package of modest FDA reforms, a key priority for Energy & Commerce Committee Chairman Fred Upton (R-MI), and a whopping $8.75 billion of new funding for NIH, a key priority for Democrats. The Senate HELP (Health, Education, Labor and Pensions) Committee has moved components of its version of this legislation, but the Senate has not voted on the package yet, largely due to a reluctance to add funds to NIH at a similar level.

The House bill would promote personalized medicine in clinical trials as well as improve research collaboration through information sharing and use of statistical and data tools. However, key provisions of priority to the pharmaceutical industry, such as enhanced intellectual property protection, were dropped on Democratic objections. No substantial item was allowed.

Moreover, the offsets in the House-passed bill (e.g., selling oil from the Strategic Petroleum Reserve and other small items that did not hit the pharmaceutical industry) were vacuumed up for other legislation that has become law, leaving a nearly $9 billion funding hole for the minority-party-demanded increase of resources to the NIH. (By the way, there is no specific plan for these funds; it's just "more.")

Rx INDUSTRY VULNERABILITY

Assuming a package is pulled together, the need for funds to offset the costs for an NIH windfall makes the pharma industry vulnerable in an end-of-year package, which while benign, does not fundamentally advance any major objectives. Over the August recess, the industry has heard that Congress is mulling inclusion of two provisions impacting the pharmaceutical industry to help fund these objectives:

1. Prohibiting patent settlements, which delay generic entry
2. Reducing the use of risk evaluation mitigation strategies (REMS), also which can delay generic entry for certain products

The Preserve Access to Affordable Generics Act (S. 2019) would effectively prohibit settlements between brand-name and generic companies that delay generic market entry when a brand-name product goes off patent. The FTC noted 145 such agreements in 2013 and many more since then, though they have dropped off recently. The legislation sponsored by Sens. Amy Klobuchar (D-MN) and Charles Grassley (R-IA) would empower the FTC to deem such agreements as presumptively anticompetitive and unlawful and enable it to levy civil penalties up to three times the gross revenue of the NDA holder during the period of violation and forfeit the ANDA (abbreviated new drug application) applicant's 180-day exclusivity eligibility. The Congressional Budget Office scored this as saving $2.6 billion over 10 years, and because of the recent higher scrutiny by FTC on these arrangements, this seems like rather free money.

In June, Judiciary Chairman Grassley and ranking member Patrick Leahey (D-VT) introduced legislation, which is intended to prohibit the use of REMS in order to inappropriately delay generic entry. The bill addresses both the availability of a reference product sample when a product is either subject to a REMS with elements to assure safe use or is under a self-imposed restricted distribution system and shared REMS negotiations. The availability of product sample for reference products have been the subject of increasing litigation and also garnered the attention of the FTC.

Attorneys at Hyman Phelps explain, "The bill addresses both ends of the generic drug [and biological product] spectrum: the availability of reference product sample needed to conduct bioequivalence studies (or other testing) in order for a company to *submit* an ANDA and the negotiations that surround finalization of a REMS program needed to *approve* a generic drug application."

Many in the pharmaceutical industry are poised to reject these two provisions, particularly since there is little to gain from enhanced funding to the NIH or public health objectives of addressing Zika proliferation and opioid abuse. But even the industry's champions are growing weary of the pharmaceutical industry's refusal to help finance congressional health priorities since enactment of the Affordable Care Act.

A clear solution would be to utilize the dedicated appropriations process to fund these initiatives. Of course, that will force Congress to make trade-offs with other pressing priorities and determine which items can be funded under current resources and which may need "emergency supplemental funding," which is not subject to budget caps. Finally, Congress should assess whether pumping another $9 billion into a federal agency is the best use of taxpayer dollars, or if the same goals can be achieved through private sector research and development. L

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

bioproduction

Single use Cell culture Purification Analytics

ALL IN

PERFORMANCE

EXPERTISE

SUPPORT

Fully invested in single-use technologies you can trust

Driving optimal efficiency takes getting the right equipment specified to your unique needs. At Thermo Fisher Scientific, we continually invest in technology and R&D to provide the most innovative and widest breadth of single-use systems that adapt to the way you work. When you need reliable service, and assurance of supply for your upstream and downstream single-use bioproduction systems, we're the partner you can count on to go all in.

Get the right solution at **thermofisher.com/sut**

ThermoFisher SCIENTIFIC

Drug Company Discovery & Commercialization: *An Election Year Analogy*

STEFAN WEBER CEO and Executive Director, Newron Pharmaceuticals SpA

When smaller, boutique drug companies move from precommercial discovery to postcommercial marketing, they can experience a shock. Precommercial work is typically rigorous and controlled with trials conducted in sequential fashion and oversight done by recognized governing bodies. Of course there can be detours along the way, but generally speaking, the path itself is well-known. In contrast, postcommercial work expands the ecosystem and, therefore, brings with it an increasing number of participants, functions, relationships, and unknowns.

As a CEO of a biopharmaceutical company, I have experienced both ends of the spectrum. We are an Italian biopharmaceutical company that is listed on the Swiss exchange, and we have an approved drug for Parkinson's disease that is sold in countries throughout the European Union and beyond. We also have a pipeline of orphan disease drugs that are still in the precommercial stage. And did I mention I am a German citizen? One who is watching the U.S. presidential election with great interest.

As I consider the move from clinical to commercialization, it reminds me of the American electoral system – primary elections that are tightly focused and a general election where a candidate faces a vastly broader audience and has the opportunity to engage on a much larger stage and with far greater impact.

PRECOMMERCIAL: THE PRIMARY ELECTION

Entering The Race — Just as a candidate entering a primary must be prepared to answer the questions, "Why are you running, what is your expertise?", so too must a biopharmaceutical company stand ready to explain its overall raison d'etre. The answer may be expertise around a disease, platform, molecule, or approach. Whatever it is, the CEO must ensure a credible tagline to support the company's existence.

A Crowded Field — As with primary elections, drug development can be a very crowded field. For example, there were 2,463 abstracts presented at this year's ASCO annual meeting. Of course that's a much larger number than 16, which is how many people ran to be the nominee of the Republican Party this year. In either case, though, the need to differentiate is essential. Drug candidates and primary election candidates alike must strive to ensure their audience understands the unique value they offer. This goes beyond the big-picture tagline. For instance, with a drug candidate, you have to prove how it is better than the standard of care. What improvement does it or the company offer? Perhaps your company works with a new chemical entity or is proposing a treatment for a previously untreatable symptom. Whether your platform is in the field of general biopharmaceuticals or targeted orphan diseases, it is critical to help your audience understand how you're different and why they should care.

A Controlled Environment — When a company is precommercial, the focus is more intimate. There is a small group of thinkers and researchers working together, knowing that they will eventually have to reach a broader audience. This stage is self-directed and exclusive; only invited partners and participants are engaged. This is the opportune time to work out any internal disagreements. With political campaigns, conflicting advice comes from numerous *experts*. For drug development companies, there may be conflicting opinions on which assets to develop or which funding sources to tap. Make these decisions in the relative privacy of the research environment, because once you reach commercialization, the stakes are higher, and the lights are much brighter.

LET'S MAKE MIRACLES

WITH ALTHEA, YOU HAVE THE POWER TO MAKE.

You have the power to make a difference. To make new therapeutics that improve quality of life and inspire a healthier world. To do this, you need a manufacturing partner who embraces your every challenge as its own, who shares your unwavering tenacity and dedication from clinical studies through commercial success. That's The Power To Make.

CONTRACT MANUFACTURING:

- Development
- Drug Substance
- Drug Product

WHAT DO YOU WANT TO MAKE?

www.AltheaCMO.com

ALTHEA | THE POWER TO MAKE™

A MEMBER OF THE AJINOMOTO GROUP

A More Focused Audience — Throughout the U.S. primary, we heard the phrases "play to the base" and "be prepared to pivot for the general election." Candidates were designated as having certain "lanes," with their stump speeches directed to segmented audiences. Likewise, as a biopharmaceutical company, the conversations we have around our pipeline drugs are very detailed, laden with scientific insight designed for an audience of experts (in our case, the field of CNS diseases). As such, we strive to include our chief medical officer in conversations with all of our different audiences — not just scientific groups, but also financial and advocacy communities.

Expect The Unexpected — There are very few pundits who can legitimately claim to have picked the nominees for the two major parties ahead of time. Sometimes the party favorite won a state's primary, but not always. This is true in drug discovery as well. Favored assets may make it to the finish line, and some do not. A good CEO will work hard to ensure there is no emotional attachment involved when allocating resources.

COMMERCIALIZATION: THE GENERAL ELECTION

Pivoting To Broader Audience — After an asset is studied and approved, it is time for its introduction to the market through the commercialization process. Compare this product launch with that of a presidential candidate. Following the party's nomination, the candidate must be ready for the national stage. As the saying goes, you only get one chance to make a first impression. Thus, it is critical to devote the time and resources for a seamless rollout, with a marketing and medical strategy designed to reach a much larger market.

Selecting A Partner — Americans seem to spend more time talking about vice president candidates *before* they are selected than at any time afterwards. This is hugely different from boutique biopharmaceutical companies that may choose a partner to market their drugs. Think carefully about whom you choose to lead your commercialization efforts — a big company with a large portfolio of drugs, a midsize company with a moderate portfolio, or a small company with a smaller, but more focused, offering. Choose the one that most closely aligns with your company profile.

Launching The Campaign — For the eventual nominee, it is time to roll out the campaign. Which states offer the best opportunity? What message should be used and through which channels? Where does the candidate spend time in person, and where are they better served sending a surrogate? For approved drugs, there are comparable considerations. In which countries should the product be offered first? What are the publications, and who are the key opinion leaders? For a company launching a commercial asset, there are now more players and more decisions.

Managing The Unknown — There are also more unknowns. A presidential candidate cannot know in advance what events on the national or world stage may upstage the campaign. Similarly, a biopharma with a newly approved drug cannot foresee events on the scientific or regulatory front that may overlap a product launch. The key, therefore, is scenario planning up front, with flexibility built into the overall plan.

"Make these decisions in the relative privacy of the research environment, because once you reach commercialization, the stakes are higher, and the lights are much brighter."

Hindsight Is 20/20 — U.S. presidential elections seem to attract an infinite number of pundits and advisors. There is no barrier to entry and no penalty for being wrong (see above: How many pundits can lay advance claim to having picked the nominees for the two major parties?). Similarly, the world of drug development and commercialization is full of advisors, analysts, and any number of people waiting to tell you what you did wrong — after the fact. As CEO, you have the opportunity to look forward. Hire the best talent in advance, and let them deploy their best ideas.

All developments in the biopharmaceutical industry start with an idea, just as primary elections begin with a candidate. Those ideas are shared with a small group of trusted advisors, and the message is directed and controlled to an identified group of followers. We see this in the election process, in which primary elections serve to narrow the field of candidates just as assets are winnowed down in the precommercial stage of drug development to be studied and brought to market.

Whether launching a new drug or electing a president, both tracks start off small and aim for big results — either general election or commercial success. L

STEFAN WEBER has led Newron since 2012 as the company's CEO and executive director, having joined the company in 2005 as CFO. Mr. Weber's background includes close to 30 years of biopharmaceutical experience across public and private companies.

VISIT US AT BOOTH #512
September 28-29 at the CDISC International Interchange

Looking for an experienced and collaborative research partner? **Chiltern is Designed Around You®.**

At Chiltern you are key, because you are at the center of what we do. As you strive every day to bring better, more personalized products to market for your patients, we strive to provide you a better, more personalized experience than any other CRO.

We're building clinical development solutions around you — your program, your investigators, your patients.
Chiltern. A Collaborative Approach Designed Around You®.

CHILTERN
Designed Around You®

Connect with Chiltern

U.S. +1 910 338 4760
Europe +44 0 1753 512 000
Chiltern.com

Clinical Development • Medical & Scientific Affairs • Data & Analysis • Pharmacovigilance
Strategic Regulatory • Clinical Supplies

LUC DEBRUYNE
President, GSK Vaccines

WILL GSK'S DEAL WITH NOVARTIS PAY OFF FOR ITS VACCINE ASPIRATIONS?

ROB WRIGHT Chief Editor @RFWrightLSL

In April 2014, GlaxoSmithKline and Novartis inked a megadeal unlike any in biopharmaceutical history. First, the two created a joint venture consumer healthcare business. A second part of the deal involved GSK divesting its marketed oncology portfolio and related R&D activities to its AKT inhibitor, as well as the granting of commercialization partner rights for future oncology products to Novartis for $16 billion. (For more on this, be sure to check out *Is Oncology Back At GSK? Did It Ever Leave?* on page 25). The third component included GSK's acquisition of the Novartis global vaccines business (excluding influenza vaccines) for $5.25 billion, an amount nearly equal to the unit's total sales revenue for 2015 ($5.38 billion)!

And although the company has been in the vaccine business for a long time, the increased responsibility that results from supplying vaccines to 90 percent of the world's countries is an obligation Luc Debruyne, president of GSK Vaccines, does not take lightly. "When it comes to vaccines, if you don't have scale, you just can't be operationally effective," says Debruyne. With over 16,000 people, three R&D centers, and 17 manufacturing sites making up GSK's vaccine business, the company certainly has scale. Following Debruyne's participation as a speaker at this year's BIO International Convention, he took time out to share how the Novartis vaccine integration has been going, as well as why GSK sees vaccines as a growth opportunity — when so many others don't.

WHY THE MASS EXODUS FROM THE BUSINESS OF VACCINES

Despite the global value of vaccines currently exceeding $34 billion (a number expected to reach nearly $100 billion by 2025), more companies have been opting to exit rather than enter the business of vaccinology (e.g.. two-thirds of the world's vaccines are supplied by just four companies — GSK, Merck, Pfizer, and Sanofi Pasteur). Even countries are exiting the vaccine business. "Today, [June 7, 2016], it was announced that AJ Biologics was acquiring Denmark's state-owned SSI vaccine production business," shares Debruyne. "Back in 2012, the Netherlands Vaccine Institute was sold."

According to Debruyne, the reason for the exodus of companies and small countries from vaccines is that to be profitable requires huge capital investments. "To give you an idea," he shares, "over the last 10 years, GSK has invested $4 billion in vaccine infrastructure." Another barrier to remaining in or entering into vaccinology is the lengthy timelines. "We've invested a total of £700 million (≈ $932 million) in two facilities in Belgium for pertussis and inactivated polio virus (IPV)," he explains. "The groundbreaking was in 2009, and the first commercial vaccine won't roll out until 2018. Few companies or countries can afford to invest so much capital and wait so long before seeing any type of return. You really need to be the size of a company like GSK, with a diversity of revenue streams, to be able to make those types of large investments with long-time horizons." GSK Vaccines began integrating the acquired Novartis vaccines business in 2015 and in May of that year stated it expected to reach a 30+ percent margin by 2020 (on mid- to high-single-digit sales growth on a CAGR basis at constant exchange rates). Some analysts estimate the profit margins for vaccines at Big Pharma companies to range between 10 and just over 40 percent. And although the business of vaccines is big money, when compared to the trillion-dollar worldwide biopharmaceutical industry, it represents a mere 2 to 3 percent.

Some argue that many companies have shied away from vaccines to focus on developing more-profitable drugs, because, historically, vaccines have been produced at relatively low prices and sold with low profit margins. But there are many pros to being in the business of vaccines. From a human health standpoint, "Nothing but clean drinking water can compete with vaccines as far as overall societal value," Debruyne attests. "One dollar of investment in vaccines returns $44 to society." A study looking at the benefits of vaccination in the United States between 1994 and 2013 estimated direct cost net savings of $295 billion and $1.38 trillion in total societal costs (i.e., the total cost to a society that includes private costs plus any external costs).

> "UNLIKE IN PHARMA WHERE YOU HAVE TO MAKE BACK YOUR PROFIT BEFORE LOSS OF PATENT EXCLUSIVITY AND GENERIC INCURSION, IN VACCINES THERE ARE NO PATENT CLIFFS TO FALL OFF."

LUC DEBRUYNE (right) with *Life Science Leader* Chief Editor Rob Wright

ONE COMPANY'S BARRIER CAN BE ANOTHER'S COMPETITIVE ADVANTAGE

Though there are many factors that make vaccines tricky (e.g., live vaccines can be troublesome to manufacture) and other barriers to entry (e.g., public agencies buying vaccines at capped prices), for those that know what they are doing, these same challenges can prove to be a competitive advantage. For example, in the U.S., Merck is the only company licensed to offer the measles vaccine and, consequently, has a captive market with about 50 percent of the purchases of its measles, mumps, and rubella (MMR) combination vaccine being made via the government's Vaccine for Children Program.

"Unlike in pharma where you have to make back your profit before loss of patent exclusivity and generic incursion, in vaccines there are no patent cliffs to fall off," Debruyne shares. "Most of the 39 vaccines GSK has on the market were discovered 20 years ago." There's an extra layer of complexity beyond that of pharmaceuticals. "In vaccines, we're talking about living viruses — bacteria," he emphasizes. "For instance, if you know anything about malaria, it's caused by a parasite, which is genetically complex. So producing a vaccine against malaria, which took us 30 years, is much more involved than producing monoclonal antibodies."

Debruyne notes that when Novartis owned the vaccine business, they were actually losing money. "But our commercial model is completely different," he states. "Theirs was a single unit with its own commercial structure, and they didn't have the power to negotiate." Because vaccines are a public health issue, ministries of health are usually very interested in negotiating with vaccine manufacturers. According to Debruyne, the GSK model uses general managers who have the whole portfolio of company products at their disposal, not just vaccines. "We have country executive boards," he says. "As such, for a government, there is only one GSK, and public health is very high on their negotiation agenda." For example, for bacterial meningitis B, GSK had the vaccine, the data, and even approval in Europe. "The U.K. has the highest epidemiology of meningitis B. Just four weeks after we [GSK] closed the deal [with Novartis], we signed a partnership agreement with the U.K. government on a fair price. The U.K. is on track to vaccinate nearly 700,000 infants every year, and this effort will generate effectiveness data for other countries," says Debruyne.

WHY GSK IS GOING AGAINST THE VACCINE EXODUS CRAZE

Debruyne has seen his share of M&As throughout his 30-plus-year career. And although he admits that M&As always require a big effort to successfully integrate, he views the Novartis acquisition as being quite unique because it involved three separate components. "We had a clear objective for why we wanted to acquire Novartis vaccines," he says. "Of course, this was part of a much bigger deal with the consumer healthcare joint-venture creation and the oncology swap, but for years we realized we were held captive by Novartis with regard to their production of diphtheria tetanus (DT) in Marburg, Germany. As a vaccine manufacturer, to be dependent on the most important component necessary to manufacture key products is not a good place to be."

Though DT was an important component of the deal with Novartis, there were other elements to consider,

such as getting one of the industry's top vaccine minds, Rino Rappuoli, Ph.D., who invented the reverse vaccinology process that resulted in the development of the first meningococcal B (MenB) vaccine, BEXSERO. (For more on this, be sure to read *How GSK Vaccines' CSO Solved The Unsolvable — The Story Of Reverse Vaccinology* on page 28). "But they also had their GMMA [generalized modules for membrane antigens] technology, as well as their self-amplifying mRNA [messenger ribonucleic acid] platforms," Debruyne attests. "GSK's goal wasn't to take on the assets and then kick out all the infrastructure. It wasn't just the complementary science that made the deal so appealing. It was the scientists — the people." Another reason the Novartis vaccine acquisition made such good business sense was the United States was an area, at least when it came to vaccines, where GSK had been lagging. "With the Novartis acquisition, we immediately laid our hands on the BEXSERO and MENVEO, so we now have the full alphabet of meningitis vaccines that cover A, B, C, W, and Y [meningitis strains]," he says. Although GSK had two of its own legacy meningitis vaccines — Nimenrix and Mencevax (divested to Pfizer in June 2015 to meet concerns raised by antitrust regulators) — these covered the same meningitis strains (i.e., A, C, W-135, and Y). And while available in 61 and 79 countries respectively, neither legacy vaccine was approved for the states. "Nimenrix might be in the U.S. by 2021 or 2022," he affirms. "The acquisition of the Novartis assets gave us immediate access to the U.S. and allowed us to accelerate our U.S. market focus." Beyond access to the U.S., Debruyne believes the science and scientists gained from Novartis would allow GSK to also accelerate its own vaccine innovation. But as is often the case when it comes to successful integration during an M&A, it is the people component that can be the most challenging.

DON'T BE ARROGANT DURING AN INTEGRATION

With any M&A, there's always the chance for duplication. For example, GSK and Novartis both had respiratory syncytial virus (RSV) programs. "RSV is an unmet medical need killing many babies just after they are born," explains Debruyne. "During the integration, we used our best scientists to determine the best RSV program to take forward and tried to make clear choices." He says vaccine R&D programs, such as RSV, were integrated at a moderate speed, taking 12 to 15 months, while integra-

tion of commercial operations were done more rapidly, lasting 6 to 9 months. "With regard to manufacturing, a key objective was business continuity," he says. "Doctors and governments don't want to be told that you can't deliver a vaccine on time because you are integrating two large companies. Integrating sounds straightforward, but it's not that easy, as global supply networks are usually long-term agreements." For this reason, integration of the Novartis vaccine manufacturing operations is deliberately being done slowly. According to Debruyne, multinational corporations can sometimes be arrogant when it comes to M&A integration. "They look at it and say, 'I know how to do this. Just plug their system into ours and run with it.' When it comes to manufacturing, you can lose a lot and make errors by not taking the time to understand how things operate."

The downside of taking too much time during integration is the impact on employees. "As leaders, we often think we need to tell employees all of the specific details regarding an M&A. But what they really want to know is if they will have a job, will it be the same as what they have been doing, and who will be their boss." Communications is a challenge, and something Debruyne admits to always being able to improve upon, especially during an integration. "When you are assigning and selecting employees, if you are not careful, it can take on a tone that's overly transactional," he states. "But you have to keep in mind: Of 10 people who may have to leave a company, at least nine are very good at what they do." To better facilitate communication during the integration, Debruyne split his management team in two — one group focused only on the integration process, and the other dedicated to executing the day-to-day business operations. He retained oversight across the two groups. During the acquisition, Debruyne constantly reminded his team of the business objectives behind the integration (e.g., accelerate access to the U.S. market). He says in situations like this, it is always good to remind yourself — and your team — why you did the acquisition in the first place. Remember what the principles of the integration were, and stay focused on always executing on those. For example, he talks about the challenge of integrating two disparate ERP (enterprise resource planning) systems. "Yes, you want to go to one system, but for quality and business continuity purposes, you can't just block each other [i.e., the two companies that are merging] from having access to each ERP," he states. "That's why we decided, for the time being, to let each system run separately. The biggest challenge of an integration isn't the hard wiring, but how an *organization* is wired culturally."

When asked what, if anything, he would do differently during the integration, Debruyne replies, "Communicate." GSK's vaccine president believes they did a great job on communicating to the people coming on board from Novartis. However, where they misstepped was with the folks from GSK. "We viewed the integration as being very synergistic and knew that most of GSK's vaccine employees wouldn't be touched," he explains. "But they didn't know this and were watching us give lots of attention to the newcomers. We shouldn't have taken our GSK teams for granted." Debruyne says, with hindsight, that is one reason why the company is now reinvesting in employee communication and engagement efforts.

One thing he would not do differently is constantly reminding employees of GSK's values. "I never started a meeting without mentioning our corporate values — TRIP: transparency, respect for people, integrity, and patients," he attests. "Getting people to focus on values is very helpful during the employee appointment and selection process. When people leave a company, how they are treated is reflected back on those who stay. You need people who are inspired to bring their very best. If an employee recently had a friend let go as a result of an M&A, and their perception is that person wasn't valued, it can be very demotivational." Debruyne says that how you treat people is the shadow your company casts, and that shadow not only impacts employee retention, but future recruitment as well.

SECURING SUPPLY REQUIRES LOOKING OUTSIDE YOUR INDUSTRY

You are probably aware of the serialization initiative being undertaken to improve the security of the biopharmaceutical industry's global supply chain. However, until serialization becomes a global reality, to help ensure the safety of GSK vaccines in areas ripe with counterfeit drugs, GSK partnered with nontraditional industry companies (e.g., Vodafone) for solutions. "If you are in Mozambique, an area where we completed a pilot program, you can just scan the bar code of a vaccine vial with your mobile phone, and you will know exactly if it is a GSK vaccine or not," explains Luc Debruyne, president of GSK Vaccines. But the collaboration goes beyond just ensuring product authenticity. The one-year pilot, supported by the Save the Children charity, also registered mothers on a ministry of health database that could alert them to the availability of vaccinations, as well as allow them to schedule appointments via text messaging. At the same time as the creation of the GSK/Vodafone partnership, the mobile communications giant also created a deal with Gavi, the Vaccine Alliance, to help collect information about how many children have been vaccinated, while also providing reminders to users of when vaccine boosters are due.

"We have 115 active scientific collaborations," Debruyne boasts. "As our ambition is to be leading the industry in the world of vaccines, it requires more than developing internal skills and expertise. It means enabling scientists to be able to see opportunities faster than anyone else." While collaborations certainly help GSK in its global health mission, they also provide employees increased visibility outside the walls of their own organization.

IS ONCOLOGY BACK AT GSK? DID IT EVER LEAVE?

ROB WRIGHT Chief Editor @RFWrightLSL

AXEL HOOS, M.D., PH.D.
SVP, Therapeutic Area Head for Oncology R&D and Head of Immuno-Oncology, GSK

Axel Hoos, M.D., Ph.D., is probably one of the biggest names in cancer drug development. After all, his scientific leadership not only led to a new paradigm for how to create cancer immunotherapies, but his development of ipilimumab while at Bristol-Myers Squibb (BMS) helped launch the entire immuno-oncology (IO) field! That being said, when the *Wall Street Journal* ran the April 22, 2014, headline, "Glaxo Exits Cancer Drugs," one has to wonder if Hoos (who joined the company in 2012 and is the SVP, therapeutic area head for oncology R&D and head of immuno-oncology) suddenly regretted his most recent career move. If GSK was truly exiting oncology drug development, would they still need him? While Hoos attests, "Oncology is back at GSK," the truth of the matter is that it actually never left. Though the mammoth deal included GSK shedding its marketed oncology portfolio and related R&D activities for $16 billion to Novartis, it also included a contractual obligation called a right of first negotiation (ROFN). This basically means that if GSK files an oncology R&D program for regulatory approval, it needs to first be shown to Novartis. In other words,

despite various media outlets arguing to the contrary, GSK isn't walking away from one of biopharmaceutical's biggest and fastest-growing markets (i.e., cancer drugs), but, instead, transforming its oncology R&D engine.

OUT WITH THE OLD — TO FOCUS ON THAT WHICH IS NEW

Sometimes it is tough to let things go, especially when it means getting rid of revenue-generating oncology assets. But if you want to be able to focus on oncology's R&D future, a divestiture can add more than just billions of dollars to your books. "You are not only shedding products that are on the market. You are removing some commercial and development infrastructure," Hoos explains. One of the benefits of the GSK oncology divestiture to Novartis is it provides focus. "GSK is not going to reenter research areas that were just divested (i.e., targeted therapy discovery and development)," he states. This is good, because in the field of oncology there are constantly new mechanisms being explored, with the biggest and fastest-growing being IO. "This is where GSK wants to place its bets," Hoos affirms.

In addition to IO and epigenetics, GSK also plans to focus on cell and gene therapy (CGT). But because CGT is highly complex, it requires a different business approach. "Technically, CGT is immunotherapy," he clarifies. "However, from an infrastructure perspective, it is very unique, because to make it work, it requires many diverse resources." This is why GSK opted not to have cell and gene therapy R&D initiatives subsumed under immunotherapy or immuno-oncology, but established its own parallel unit within the Oncology Therapeutic Area.

Another benefit Hoos sees from divesting the marketed oncology medicines is that it gives GSK the room to come up with new waves of innovation, as those former medicines are no longer taking up the resources. "When you think about how much money goes into product lifecycle management (PLM) [i.e., marketing, label expansion] relative to discovery and development [i.e., R&D], it can be a significant portion of your overall budget," he says. Hoos notes that the divestiture also eliminated internal R&D competition. "When I arrived at GSK, new oncology discovery performance units (DPUs) [which are discussed in detail later in this article] were competing for resources with other, more-established parts of the business (e.g., small molecules for tyrosine-kinase inhibition and BRAF and MEK inhibitors)," he states.

When Hoos landed at GSK, throughout the biopharmaceutical industry, "generation two" of immuno-oncology R&D was well under way. As his previous work at BMS (i.e., ipilimumab) represented "generation one," if he wanted to build something from scratch, GSK would basically have to skip working on a generation of IO drug development. "There were at least 15 PD-1s being developed," he shares. "As all the PD-1 and PD-L1-blocking agents represented IO generation two, we knew that everyone else was pretty much already there." Rather than try to play generation two catch-up, GSK instead opted to focus on generation three via its DPU approach.

HOW GSK IS PREVENTING R&D INITIATIVES FROM BECOMING KNOWLEDGE SILOS

"What often happens at Big Pharma companies is you unintentionally end up siloing certain activities," says Axel Hoos, M.D., Ph.D. "This was something we recognized not long ago. Perhaps you have oncology and infectious diseases therapeutic areas that share certain features and work on mechanisms that are similar, but may not know what each other is doing. So what do you do to break down those silos?" For GSK the approach was to create an overarching R&D focus based on immunology because "the immune system basically has universal mechanisms that can be applied in other R&D areas," explains Hoos, who is GSK's SVP therapeutic area head for oncology R&D and head of immuno-oncology.

The immunology framework designed to cross-pollinate R&D ideas (aka break down silos) and share knowledge throughout GSK is called the Immunology Summit, and it includes external academic experts and entrepreneurs who serve as advisors. While immunology is a core GSK focus (e.g., vaccines), it is important in many other areas as well. "You can apply that universal mechanism to cancer, an infectious disease threat, bacteria, as well as a virus," he asserts. "Perhaps a PD-1 could work in HIV and doesn't have to be restricted to just oncology." According to Hoos, out of the eight GSK therapeutic areas, immunology touches almost all of them. So why not seize it as an opportunity to cross-pollinate and elevate ideas?

HOW GSK CREATES SMALL BIOTECHS WITHIN A BIG PHARMA

Although the transaction was complex (as well as expensive), because GSK sold its marketed-oncology products for a premium (i.e., 10 times their annual sales), the company is able to reinvest some of those funds and basically "rebuild" its oncology business, which it is doing using DPUs. "The DPU model is actually one of the things that attracted me to GSK, because it enables you to be more entrepreneurial with a focus on one area of science," Hoos states. At GSK, a DPU is treated like a small biotech company within the structure of a large pharma.

The process of creating a DPU — which GSK/Hoos did for immuno-oncology — involves developing a business plan that is presented to governance for review and, if approved, funded for a three-year cycle. "While a DPU may have some touchpoints to assess if it's working or not, like a small biotech, you are in charge of your own budget and deliverables, and the structure allows you to work beyond just doing in-house discovery," he states.

For example, if building in an area of science where there exists a technology that would benefit the DPU's vision, the DPU can make an acquisition, develop an in-licensing deal, or create a partnership that enables it to build a portfolio. "We do a lot of option deals with milestones, and, if achieved, we can opt to buy the technology," he attests. This is why Hoos views the DPU approach as an excellent means of de-risking R&D. "It allows you to work closely with other companies that have specific expertise, rather than spending a lot of money up front to acquire it, thereby diversifying what you are able to do."

A DPU head — functioning like a CEO of a biotech —can build their own team, recruiting either internally or from GSK or outside the company. For example, the immuno-oncology DPU began with 15 GSK employees, most of whom came to the unit without having previous IO experience. "This is because the generation three IO area we were trying to build did not yet exist," Hoos says. Today, the IO DPU consists of 85 employees, not all of whom came from within GSK. The other two areas of GSK oncology science (i.e., epigenetics and cell and gene therapy) are also set up as DPUs with their own heads. However, after the closing of the Novartis transaction, GSK is now rebuilding the Oncology Therapeutic Area with these three DPUs as building blocks. While GSK's structure results in DPUs being treated like stand-alone, small biotechs, unlike a small biotech, these DPUs have the resources that only a Big Pharma can provide.

THE FOUR PILLARS OF GSK'S DIVERSIFIED ONCOLOGY R&D PIPELINE

There is no question that Hoos is interested in creating at GSK the same kind of transformational drug he worked on at BMS. "Right now, I'm focused on building something that is different and diversified," he says. The first part — or "pillar" — of the plan to create the immuno-oncology R&D pipeline was to establish a set of checkpoint modulating antibodies of the third generation. Two of these are already in the clinic — an agonistic antibody against OX40 [CD134] and an agonistic antibody against the inducible co-stimulator (ICOS).

The second pipeline pillar is bispecific antibodies (i.e., putting two targets into one molecule). "Instead of having the antibody bind to one thing, you can have an antibody bind two things, and with that you end up having a combination therapy in one molecule," he reiterates. While this is still in the discovery science phase, Hoos

attests to GSK working on three different platforms of bispecific antibodies.

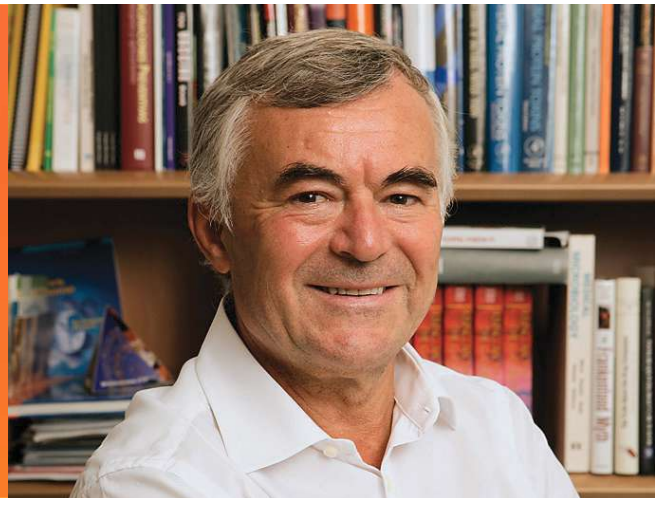
The third pillar involves small molecules. "We are leveraging our small molecule expertise and focusing it on immunotherapy targets, which is basically an unused area," he says. Last year Hoos and three of his colleagues (Jerry Adams, James Smothers, and Roopa Srinivasan) wrote an article (*Big Opportunities for Small Molecules in Immuno-oncology*) published in *Nature Reviews* (July 2015) about how to use small molecules in immuno-oncology. He says the article was well-received and sets a framework under which small molecules can be used to make medicines in immuno-oncology. To that end, GSK has developed a set of new small molecule immuno-oncology targets and anticipates these moving into the clinic within the next 18 months.

"The fourth pillar is actually the most challenging, as well as the most exciting — cell therapy," he says. While cell therapy is currently being attempted by many players using different approaches, at GSK it is viewed as an immuno-oncology component that needs its own infrastructure. "When I started at GSK, we built a group within the IO DPU that did cell therapy," he shares. "But now that this area is reaching critical mass, it really needs to be its own DPU if it is going to be successful, and that's what we are just starting to do." To create next-generation cellular medicines, GSK Oncology is using a modular approach with multiple technologies integrated on a central platform. This approach includes different cell carriers, targeting receptors (CARs, T-cell receptors), signaling cascades, immune checkpoint or cytokine genes, supply chain technologies, and other components. Academic and industry partners also contribute key knowledge and technologies to the central R&D effort at GSK.

After the Novartis transaction was announced, many people thought GSK had just exited the hottest therapeutic category — oncology. Hoos doesn't see it that way, though. He believes GSK seized this opportunity to transform its oncology R&D engine. "Immuno-oncology is clearly transformational, as are the checkpoint modulating antibodies currently being marketed," he avows. For GSK to transform oncology, it meant striving to be a leader in the next generation of immuno-oncology products. "It has taken us almost four years to build the current pipeline of more than 15 immuno-oncology assets, and we just put the first drugs into the clinic," he concludes. Targets and modalities were chosen to create synergies and enable novel combination therapies that may deliver transformational effects for patients. The focus remained on generation-three assets (OX40, ICOS, TCR-Ts) and not duplicating generation-two assets (PD-1, PD-L1, IDO, CD-19 CAR-T).

HOW GSK VACCINES' CSO SOLVED THE UNSOLVABLE — THE STORY OF REVERSE VACCINOLOGY

ROB WRIGHT Chief Editor @RFWrightLSL



RINO RAPPUOLI, PH.D.
Chief Science Officer, GSK Vaccines

Rino Rappuoli, Ph.D., was faced with what many considered an unsolvable puzzle. The chief science officer for GSK Vaccines wanted to discover a vaccine for a serogroup B (MenB) of meningococcal meningitis that is responsible for nearly 50 percent of all worldwide cases of the disease. "Once you have seen one case of meningococcal meningitis, you don't want to see another, and, unfortunately, I've seen too many," he laments. "The mortality rate is as high as one in four." Decades of research — as well as an unexpected encounter with a world-renowned geneticist — ultimately led Rappuoli to a solution he called reverse vaccinology.

SOLVING THE MenB PROBLEM REQUIRED SOMETHING REVOLUTIONARY

In the early 1990s, Rappuoli had developed the conjugate vaccine solution that would work for meningococcus strains A, C, Y, and W. And though his success led to a

> "WHILE MANY OTHER GROUPS CONTINUED TO TRY TO SOLVE THE MenB PROBLEM, I BASICALLY SHUT DOWN THE PROGRAM, AS IT SEEMED USELESS TO WORK ON IF WE DIDN'T HAVE A TECHNICAL SOLUTION."
>
> **RINO RAPPUOLI, PH.D.**
> Chief Science Officer, GSK Vaccines

vaccine that helped to dramatically reduce the incidence of meningitis C (MenC) in the U.K., he knew the same approach was not going to work for MenB, because of B's peculiar characteristic. "Unlike vaccines developed for serogroups A, C, W, and Y that induce an immune response against the polysaccharide capsule surrounding the bacterium, the capsular polysaccharide of MenB is structurally similar to certain abundant human glycoproteins," he explains. "Therefore, if you try the same approach in developing a vaccine for MenB, you run the risk of causing autoimmune damage, as the MenB pathogen mimics host molecules." In other words, the body's immune system views the B antigen as something that is supposed to be there and, as such, won't raise an immune response.

"While many other groups continued to try to solve the MenB problem, I basically shut down the program, as it seemed useless to work on if we didn't have a technical solution," he states. It appeared something revolutionary was needed in order to proceed. In 1995, in what Rappuoli describes as a lucky break, he stumbled across a *Science* magazine article in which Craig Venter had published the first genome sequence of a living organism. For the first time in human history, scientists were able to read what was required to make a living organism. And while Rappuoli thought this new technology might be the solution for what had previously seemed impossible (i.e., developing a MenB vaccine), he admits it took him about a year to fully conceptualize how. "I

was trying to decide if I should learn how to sequence a genome," he explains. "I calculated that for me and my team to become experts in mapping the necessary genome to solve MenB, it would take three to five years. In the end, I thought, 'Why should I learn something that other people can already do?'" So the vaccinologist decided to go talk to Venter.

Around 1996, Rappuoli visited Venter at The J. Craig Venter Institute (formerly know as The Institute for Genomic Research), and asked if he would be willing to sequence the meningococcus B genome. Venter's first reaction was, "Why should I do another bacterium when we've already done it?" Rappuoli suspected this might be his answer, as he knew mapping the bacterial genome was one small step toward eventually mapping the human genome. So he proceeded to tell Venter about the terrible disease that kills young children and adolescents that had no remedy. "I said, 'If you sequence meningococcus B, we might be able to actually make a vaccine,' and that got him to turn around," he attests. "Fifteen minutes later, we were collaborating and have been ever since." This allowed Rappuoli and his team to focus on their core knowledge of how to make vaccines instead of trying to learn how to sequence a genome — which would have wasted a lot of time.

OVERCOMING RESISTANCE AND SKEPTICISM TO REVERSE VACCINOLOGY

Rappuoli's concept of reverse vaccinology involved taking an entire pathogenic genome and screening it. Using bioinformatics, the goal was to find genes with desirable attributes that would make good vaccine targets. As Rappuoli presented the concept of reverse vaccinology, he quickly realized that it caused two problems — external scientific skepticism and internal scientist resistance. And while overcoming outsider cynicism was an eventual goal, in order to successfully do so first required defeating insider reluctance. "At the time, biology was done very differently," Rappuoli relates. "Prior to reverse vaccinology, every person working in biology, either in the company or an academic lab, was basically one person, one protein, one project." But because Rappuoli's proposal involved identifying potentially 600 proteins, under the traditional model (i.e., one person = one protein) this equated to needing 600 postdocs — each working on their own protein. That wasn't possible, because at the time when Rappuoli was trying to realize his reverse vaccinology idea, he was working at Chiron Corporation, a small biotech based in Emeryville, CA. So he pulled the team together and said, "Now we're going to work differently, like a chain, with one person working on the first piece, someone else the second, and so on." But his team's reaction was not one of receptivity. "We aren't here to be your technicians," they said. "We are scientists here to do our own experiments in an independent way." According to Rappuoli, it took six months of meetings and convincing just to overcome this internal scientific sentiment.

Around seven months into the new research approach, the team was finally to a point of being able to analyze the genome, and that's when things started to really get exciting. For example, in studying the MenB genome, they found 2,158 genes. While the team predicted that 600 had the potential to make good vaccine candidates, they ended up expressing 350, which was still significant, considering that up to this

COLLABORATING WITH CRAIG VENTER PROVES TRANSFORMATIONAL

"I know a lot of people who have started companies, but I don't know a lot of people like Craig Venter," says GSK Vaccines Chief Science Officer Rino Rappuoli. After his work on genomics, Venter became interested in synthetic biology and wished to explore the possibility of using it to develop vaccines. "When he first suggested this, I told him this was just another one of his crazy ideas," laughs Rappuoli, suddenly finding himself thrust into the role of scientific skeptic. "For the first two years, using synthetic biology as a means to develop vaccines wasn't really a fit," he affirms. "However, in the third year, things started to gel." In 2013, Rappuoli's team began working on a new potentially pandemic avian influenza strain (H7N9) that had been identified in China. It was Easter Sunday, and the Chinese CDC had just posted on its website the sequence of the two genes that were part of the H7N9 vaccine. The way vaccine seeds are usually made is a strain is identified, isolated, and sent to one of the three government centers in the world that make vaccine seeds. From there, scientists working at places like the CDC in Atlanta use the identified strain to try to make a vaccine (typically a three- to six-month process) and, once completed, give the seed to a manufacturer for commercial production. On the Monday after Easter, Venter, working in La Jolla, CA, synthesized the two genes from nucleotides. "He shipped us what we needed via express mail, and by Thursday of that same week, we had the first viruses popping up in the lab," Rappuoli says. By Saturday, Rappuoli's team had the necessary seed to make a vaccine. Using synthetic biology, Venter and Rappuoli converted what was typically a six-month process to about five days. "That gives you an idea of how transformational things can be when you decide to collaborate with Craig [Venter]," he concludes.

point everyone had been expressing just one at a time. From there, the team began testing the serum on mice and, within six months, had discovered 91 new proteins on the surface of the bacteria. "Prior to this, all of the microbiologists in the world had discovered only 13," he says excitedly. Though the team didn't yet know which of these was going to end up making a vaccine, they had discovered something nobody else had, which galvanized them. "From that point on, I did not have to push them, as they were actually pushing me," Rappuoli attests.

In the beginning of the project, he says they rarely spoke about reverse vaccinology outside of the organization. However, the scientist recalls presenting at a Neisseria (meningitidis) Conference where he first encountered external skepticism to reverse vaccinology. "I presented data explaining how we were using genomics to get new proteins, which was a very revolutionary concept," he reflects. "At the end, I didn't get any questions. But I do remember a comment, which was basically, 'Let's wait and see what happens.'" He says when it comes to overcoming external skepticism, the more data you publish, the more people start to believe. That being said, it wasn't until after the MenB vaccine (BEXSERO) was approved in Europe (2013) and the U.S. (2015) that skeptics really started to believe.

COULD REVERSE VACCINOLOGY RESULT IN A NOBEL PRIZE?

As the conversation with Dr. Rappuoli winds down, I ask if he has ever thought that his work on reverse vaccinology might result in a Nobel Prize. "No," he responds quickly. "My priority in developing vaccines wasn't winning an award but dealing with a severe disease. My passion for focusing on meningitis was nurtured from my training at Rockefeller University under Emil Gotschlich." According to Rappuoli, there is not a tradition of Nobel Prizes being awarded for successful vaccine development. In fact, in the 121-year history of the award, only one vaccine scientist has ever been awarded the Nobel Prize for physiology or medicine (i.e., Max Theiler for his work on developing a Yellow Fever vaccine). But awards aren't what give the GSK Vaccines chief science officer satisfaction. It's simply protecting people from disease. "We are eager to see the U.K. results, where all of the newborns have been immunized, to get a feel for the impact the BEXSERO vaccine is having on the disease," he says. Thus far, the best results come from the Canadian region with the highest incidence of meningococcus B. "In May 2014, the Saguenay-Lac-Saint-Jean region in Quebec began vaccinating the entire population from two months to 20 years of age with BEXSERO," he explains. "Since they began immunization and up to the last report a few months ago, they've had no more cases of MenB in those who have had the vaccine." Results like these, more than Nobel Prizes, reinforce that his effort to pioneer reverse vaccinology was time well spent.

CANCER IMMUNOTHERAPY

SIMPLER OR MORE COMPLEX?

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

There comes a time when the present can no longer be described in terms of the past. A great leap forward redefines our normal experience and resets our expectations. We must invent and adopt a new lexicon for the future. And yet the transformation can happen silently, invisibly, and unfelt right in front of us, leaving the past behind like a vaporous dream.

Such a change of scene is happening right now, in the form of cancer immunotherapy. You won't see much about it in the general press or on the nightly news, and even the central players in this dramatic shift seem to be doing their best to keep a lid on things in one way or another. But slowly and surely, the wheel is turning, and when we look back from the future, we will see that cancer treatment has made a giant leap forward with immuno-oncology (IO).

Two years ago (September 2014 issue), we initiated a five-part series that captured the thoughts of many key IO players and anticipated most of the issues the field faces even today. A "virtual roundtable" of a dozen key opinion leaders, including some of the main pioneers in IO drug research and development, along with executives in 16 companies conducting clinical trials in the space, contributed their views and expertise to the series. We then followed with an update a year later (September 2015 issue) on the current clinical results and insights.

The series and update shed light on how science can drive business in the life sciences industry. Companies have scrambled to keep up with the emerging science of cancer immunotherapy, and the articles in this series supply an essential layperson's understanding

of the scientific progress in IO and its course-changing effects on the IO business space.

This year, with most of the major cancer meetings concluded, yet so much in the IO space still in full flux, we are turning to someone who first proposed, then served as moderator of, the virtual roundtable in the original "Combination Cancer Immunotherapy" series: Llew Keltner, M.D., Ph.D. Keltner is an oncologist long active in drug development, company startups, and partnerships in the cancer space, particularly in immuno-oncology. He continues to be an ever-present witness and participant in the IO arena, constantly interacting with scientific and business leaders working on the remarkable new generation of cancer immunotherapy approaches.

"Anti-PD-1/anti-PD-L1 is the backbone of cancer immunotherapy, except in some very unusual situations."

LLEW KELTNER, M.D., PH.D.

RUNNING HOT & COLD

In the following exchange, Keltner sums up the key issues and findings that fired up the IO field during the past year. He reports on new clinical trial results and evolving theories about immunotherapeutic mechanisms and agents in cancer, as presented at the leading oncology meetings and discussed in the IO community. In many cases, the new findings bear out predictions made in our original series; in other cases, they challenge previous expectations. Safe to say — in most cases, controversy among the various players in the field continues despite, or because of, the new insights, and Keltner expresses his own views as well.

WHAT WERE THE AREAS OF EMERGING CONSENSUS IN IMMUNO-ONCOLOGY DURING THE PAST YEAR?

KELTNER: The bottom line, which became clear at the AACR (American Association for Cancer Research) annual meeting, and was even more clear at ASCO (American Society of Clinical Oncology), is that anti-PD-1/anti-PD-L1 is the backbone of cancer immunotherapy, except in some very unusual situations. More money has been spent on development of anti-PD-1 drugs, by about a factor of three, than any other type of drug in history. We now have more than 100 anti-PD-1s, and more than 30 anti-PD-L1s, in development worldwide. So the reality is anti-PD-1/anti-PD-L1 therapy is the biggest focus of drug development that has ever existed.

BASED ON THE WIDER USE TO DATE, HOW DIFFERENT IS CANCER IMMUNOTHERAPY FROM OTHER TREATMENTS IN ITS RESULTS?

In specific subsets of patients with nonsmall cell lung cancer (NSCLC) treated with anti-PD-1 as a sole agent, we can hit about a 40-percent response, compared to around 10 percent with other drug treatments — and this isn't a typical progression-free survival response. When patients respond, when their tumors shrink with immunotherapy, and when they live longer than a year, they tend to respond dramatically, beyond all precedent. That is the magic of immunotherapy.

In some of Dr. Jedd Wolchock's 10-plus-year studies with anti-CTLA-4, a very high percentage of the melanoma patients who survived for a year are still alive. So response in cancer immunotherapy is completely different than what we've all thought of as a response in solid-tumor therapy with radiation, chemotherapy, antineovascular agents, and targeted agents. All of those earlier therapies can destroy tumor tissue, but they don't treat the disease very well at all, which is why they show so little improvement in overall survival, except in small trials with highly selective patient populations.

Oncologists have become accustomed to image-based response measurement and the idea that if they're killing tumor tissue it must be good. That's a nice idea, but, unfortunately, it doesn't correlate well with the patient's survival, and all of the conventional drugs — and of course radiation — have very bad side effects. With cancer immunotherapy, we are now

Change the world with UBC by your side.

Pharma Heroes around the world are fighting for patients with the help of UBC. Our slate of pharma services can help you manage a late stage research study and monitor the global safety of your product.

Learn more and recognize a Pharma Hero you know:

www.PharmaHeroes.com

PharmaHEROES℠

UBC®
AN EXPRESS SCRIPTS COMPANY

seeing what we hoped and expected to see — when patients respond to an IO drug, they have a very good potential for long-term survival.

At this year's ASCO meeting the talk was, now what do we do with survivorship? We're seeing cancer patients who, thanks to immunotherapy, are living for very long periods of time. What does that mean for us as a field? How do we treat these patients? How do we monitor these patients? What kind of follow-up is necessary? We haven't really had this problem before. It's very similar to what happened with AIDS after the protease-inhibitor cocktails came into use. Among the up to 40 percent of NSCLC patients who respond to anti-PD-1, any one of them may have a good shot at a normal lifespan, and certainly a much longer extension of life than with other drugs.

BUT WHAT ABOUT THE 60 PERCENT OF PATIENTS WITH NSCLC OR 90 PERCENT WITH PROSTATE, LIVER, OR OTHER CANCERS WHO FAIL TO BENEFIT FROM ANTI-PD-1 THERAPY ALONE?

The evidence suggests that a very important difference in the nonresponder populations is that they have low-TIL tumors; their tumors do not contain activated CD8 T cells, called tumor-infiltrating lymphocytes (TIL), so they're TIL-negative. In patients who are TIL-positive, the correlation with response to anti-PD-1/anti-PD-L1 is extremely high. In the current jargon, TIL-positive tumors are *hot* and TIL-negatives are *cold*. That idea was first discussed intensely at the SITC (Society for Immunotherapy of Cancer) meeting in the fall last year, at several IO conferences last winter, and then at AACR and ASCO this spring. Now hot and cold tumors seem to be the "hottest" thing in the field these days.

COULD THE HOT AND COLD TUMOR IDEA TRANSLATE INTO TREATMENT?

At ASCO, there were probably at least 100 presentations or abstracts related to ways to convert cold tumors into hot tumors. In general, the idea is gaining a huge amount of credibility. Much of the data seems to show that it is quite reproducible with all sorts of different mechanisms. One reason for the widespread belief in the idea is the use of biopsies in cancer-drug trials, which has just gone through the roof. Ten years ago, biopsy trials were not rare, yet not that common, but these days the number of trials that involve biopsies is just enormous.

Yet researchers are using biopsies to determine whether patients are PD-L1 positive, HER2 (human epidermal growth factor receptor 2) positive, or positive for some other marker to predict their response to a particular molecule. They typically look at gene signatures in tumors, which is unfortunately misleading because tumors are so massively heterogeneous. A needle inserted into a tumor at a particular location, at a particular moment, may sample a bunch of cells that show XYZ. Another needle in the same tumor at the same moment won't show the same thing. Tumor heterogeneity is why cancer immunotherapy works where the other forms of cancer therapy fail. A biopsy showing high or low TIL may also be more indicative, since TILs are living cells, and when appropriately activated, they can proliferate and destroy cancer cells throughout the tumor.

TARGET THE IMMUNE SYSTEM, NOT THE TUMOR. SO HOT TUMORS CONTAIN TILS, BUT THE TILS ARE STILL A COMPONENT OF THE IMMUNE SYSTEM?

Yes. It all starts with T cells. CD8 T cells, or effector T cells, are just T cells that express the receptor protein CD8 on their surface. There are progenerative T cells — immune stem cells that have the ability to go in a zillion different directions. They can become T regulatory (Treg) cells when they express the Foxp3 protein on their surface, or CD4-T cells when they express the CD4 protein on their surface.

We had always thought Tregs are bad in cancer because the tumor uses them to suppress CD8s. It turns out Tregs can stop expressing Foxp3 and start expressing CD8 and begin killing tumor cells. All T cells are capable of becoming tumor killers, or TILs. It's just a matter of expressing DNA and changing pathways and functions within the T cell, probably in response to the triggering of multiple pathways inside the cell. In general, any T cells expressing the CD8 marker are very likely TILs, and they will kill tumor tissue as long as they've been activated to one or more of the tumor antigens.

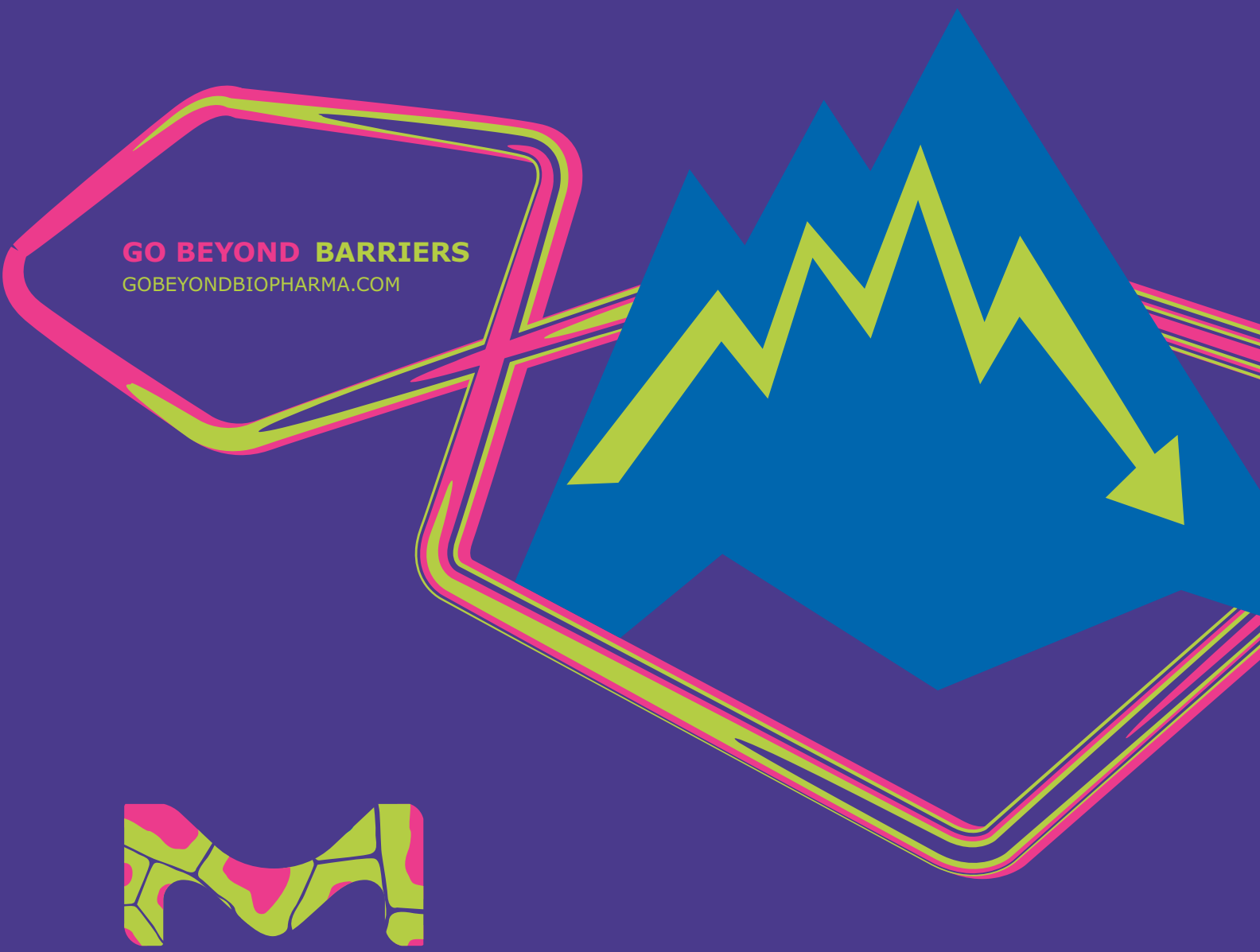
Despite all of the proposals and research on how to convert TIL-negative to TIL-positive patients, however, only a small number of commercial candidates exist. One avenue companies have explored is apoptotic ablation, which makes tumors hot by creating neo-antigen containing apoptotic bodies in the tumor that traffic to the tumor-draining lymph nodes and get

Fear of the unknown?

250 industry leaders told the Economist Intelligence Unit the biggest barriers to their growth. Want to know what they were?

Get your exclusive report today.

Visit us in Boston at BPI booth #821.



The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

MilliporeSigma

exposed to T cells. CD8-T cells get activated, wander around the body, and locate those tumor antigens on any remaining tumor or metastasized tumors. In a certain percentage of patients, you get abscopal effects — shrinking or disappearance of tumors outside the local treatment area. If the patient can then be treated with an anti-PD-1, anti-PD-L1, and/or an anti-CTLA-4 or TNFRSF (tumor necrosis factor receptor superfamily) co-stimulator, the abscopal response rate may approach 80 or 90 percent or perhaps more.

There are also a small but increasing number of cancer vaccines with data demonstrating they can convert tumors from cold to hot, but only one cancer vaccine platform, the allogeneic transfected whole tumor cell technology from Heat Biologics, has produced data from human clinical trials demonstrating the vaccine can convert 100 percent of tumors from cold to hot in multiple indications. There are lots of other agents that can help — old targeted drugs and even chemotherapies will trigger some apoptosis and immune activation in a tumor, causing conversion of a low percentage of patients from cold to hot.

But there are new therapeutic candidates out there that will do a fantastic job of it, and if the pharma companies will pick them up, push them forward, and really drive hard, we may see some dramatic developments. But we also have to be cautious; some companies that were making cytotoxic agents two years ago now say they are doing cancer immunotherapy, converting tumors from cold to hot. Maybe so — in rats or mice — but they are a long way from human proof of concept.

BEYOND THE BACKBONE?

With one approach, blocking PD-1, now dominating the IO field, work on new immunotherapy agents continues but new approaches are being almost desperately pursued. Keltner discusses some important developments with other immunotherapies, vaccines, and co-stimulators.

HOW DOES IT LOOK NOW FOR THE DEVELOPMENT OF OTHER CHECKPOINT INHIBITORS BESIDES ANTI-PD-1?

First, I don't like calling anti-PD-1 a checkpoint inhibitor. There's new data emerging that suggests

NEIL BERINSTEIN, M.D.
Professor of Medicine
University of Toronto
Odette-Sunnybrook Cancer Center

ADVANCED IN TRANSLATION

A member of the original panel of science experts and key opinion leaders in our Combination Cancer Immunotherapy virtual roundtable series (September 2014 to January 2015) responds to our query: What was the most important advance in immuno-oncology during the past year?

Advancement in translational science is the most important advance in immuno-oncology.

Now, finally, there have been successes in using the immune system to fight cancer. This follows a decade or more of failed clinical trials that told us more what not to do rather than what to do. With the clinical success of checkpoint inhibitors and some cell therapies, the situation now is different — translational science is providing significant understanding of how the new cancer immunotherapies (CIs) are working, and the field is suggesting rational science-driven strategies to further enhance these therapies.

The new insights are possible because of significant advances in technologies such as whole exome sequencing, multiplex immunohistochemistry, and gene expression profiling of clinical samples. For example, the evidence that the mutational load, lymphocytic infiltrate, and level of PD-L1 expression are predictors of response to some checkpoint inhibitors has fueled a number of hypotheses around how CIs are working and how to make them work better. From this data it is hypothesized CIs are allowing lymphocytes that recognize processed and presented neoantigens in the tumor to expand, infiltrate the tumor, and attack. Recent evidence for this includes relationships between mutational load and clinical response to CIs in melanoma and lung cancer. Moreover, cell therapy recognizing mutated neoantigens has been associated with clinical response in some patients.

More importantly, this translational data predicts that various strategies to increase tumor-specific lymphocyte infiltration into tumors should synergize with CIs. To accomplish this, strategies and trials combining CIs and vaccines, cell therapies, and local immunotherapies or cancer therapies are being initiated. Additionally, we are approaching the era where CIs or other immunomodulators may be combined with vaccines or cells generated to patient-specific neoantigens that are thought to be highly immunogenic. Given the strong translational science that has provided a rationale for these trials, there is a high likelihood of further significant advances and successes in immuno-oncology.

first BRIC ☑.
NOW...?

Explore tomorrow's biopharma landscape with the Economist Intelligence Unit. Learn about where the industry is going next.

Get your exclusive report today.

Visit us in Boston at BPI booth #821.

the most important mechanism of action of anti-PD-1 may not be its checkpoint inhibition, which interferes with the binding of PD-1 and PD-L1 on tumor cells. PD-1 is expressed by the CD8 T cells, and when they bind to the PD-1 ligand PD-L1 on the tumor cell, the CD8 T cells become inactive.

The theory was that anti-PD-1 merely blocked the process of inactivating T cells. But studies are now showing that when anti-PD-1 binds to the PD-1 on a CD8 T cell, likely all of the TNF (tumor necrosis factor) family of receptors — OX40, 4-1BB, GITR, ICOS, and especially TNFRSF25 — gets dramatically upregulated on that T cell, which causes the population of activated T cells to proliferate. That is why the TNF receptor agonists are called co-stimulators, now recognized as a new class of immunotherapeutics.

This year at ASCO, the level of excitement about the TNF family of co-stimulators did not go way up, but it didn't go down, either. Most of the community was looking at the latest clinical data for the co-stimulators, mainly anti-OX40 and anti-4-1BB. Other companies are also developing the co-stimulators, but Pfizer and Roche were the only ones to present clinical data at ASCO. AstraZeneca did not present data on their three ongoing combination studies involving anti-OX40 or the OX40 ligand fusion protein.

Some analysts and others at ASCO said the co-stimulator data was disappointing because the reported clinical responses were not overwhelming. However, these were first-in-man dose escalation studies in small numbers of patients, monitored for relatively short periods of time. Just as occurred in early trials of anti-CTLA-4, the patient responses from new immunomodulatory agents can be surprising — and in some cases can occur very late. All data suggesting the combination of the co-stimulators with anti-PD-1/anti-PD-L1 in humans is theoretical, based primarily on in-vitro and mouse tumor model research. We are in very early days, and there is an astonishing amount to learn about these agents — which are, again theoretically, not likely to have much effect as monotherapies.

The safety data for 4-1BB and OX40 was great. Many people have been worried about safety with the co-stimulators because they can have some seemingly opposing effects. OX40 and TNFRSF25 cause a large and immediate up-regulation in Tregs. That concerned those who still think Tregs are evil, but we know the greater the Treg stimulation, the more CD8 memory activity results. According to research published more than a year ago, the Tregs that accelerate immediately are required for the maturation of activated or "memory" CD8s. The research found that cytokines secreted by the Tregs are absorbed by the CD8s, pushing them to become memory CD8s, another term for TILs, which go after the tumor.

SCIENCE FIELD TO BUSINESS SPACE

As research continues to elucidate immunotherapeutic mechanisms and test new targets, corporate constraints, payer pushback, clinical challenges, and regulatory conundrums are shaping the IO business and market, for better or worse.

SO WHAT'S LEFT WITH CHECKPOINT INHIBITORS?

Anti-CTLA-4 really is one of the few actual "pure" checkpoint inhibitors out there, and the only one so far to go into the clinic, as well as the only one to be approved. Some say the IDO (Indoleamine 2,3-dioxygenase) inhibitors are checkpoint inhibitors, but they're not. They're just affecting mechanisms in tumor cells that alter the ability of T cells to survive as affected by the tryptophan breakdown pathway (tryptophan [TRP] to kynurenine [KYN] metabolic pathway). But they don't target immune checkpoints; they are probably only involved in facilitating T-cell proliferation.

Any human cell can get around an IDO inhibitor, and any cell can get around a TDO (TRP-2,3-dioxygenase 2) inhibitor. Tryptophan breakdown goes through multiple pathways in the cell, each one ending with kynurenine, which is the bad actor with T cells, sending them into apoptosis. Kynurenine is produced from tryptophan even if you block IDO completely, or if you block TDO completely. And if you block those two things completely, some researchers believe that there will be severe toxicity. One company, Kyn Therapeutics, is working on a way to cleave the kynurenine, but it's at a very early stage.

Scientists and companies propose all sorts of mechanisms for how they can affect T-cell behavior, with many related agents such as PEGylated IL-10, TIGIT (T-cell immunoreceptor with Ig [immunoglobulin], anti-TGF beta, and ITIM [immunoreceptor tyrosine-based inhibition motif] domains). But those are also not really checkpoint inhibitors. Compugen has a

therapure
BIOMANUFACTURING

Passion for your Process, Product and Patients

Development Services
Cell Line; Upstream;
Downstream; Analytical

cGMP Manufacturing
Upstream Production;
Downstream Purification

Aseptic Fill/Finish
Vials; Syringes;
Lyophilization

Contract manufacturing of biologics is more than having superior technology – it's having experienced people who are passionate, responsive and committed to developing and manufacturing your biotherapeutics to improve patient care.

We invite you to feel the difference at Therapure Biomanufacturing, where the client experience is our passion and patient care is our commitment.

Please visit us at
www.therapurebio.com/CDMO
Or contact:

Dina Iezzi
Director, Marketing & Special Projects
Phone: +1 (905) 286-6270
Mobile: +1 (647) 234-3395
Email: diezzi@therapurebio.com

slew of real checkpoint inhibitors with novel targets. Bayer has licensed two of them and is carrying the development forward, but they're not yet in the clinic. Compugen is developing its own targets and is no less than a year and a half from the clinic.

WILL THE BIG PLAYERS WITH ALREADY-APPROVED DRUGS CONTINUE TO DOMINATE THE IO SPACE?

I don't believe the patent challenges will succeed, especially if they are based on use of a natural DNA sequence. Out of the more than 100 anti-PD-1s in development, some of them will make it to market. One in particular will surely be the BeiGene product. BeiGene very likely has a "gold stamp" from the Chinese government, and patients are not in general being treated in China with Keytruda (pembrolizumab) or Opdivo (nivolumab) in a clinical trial or otherwise. The Chinese government has made it very difficult for biologics not manufactured in China to enter development for approval in China. BeiGene has developed and manufactures its drug in China as a Chinese company. But it is a public Nasdaq-listed company, now well into anti-PD-1 trials and smart as a whip, having just hired Merck's cancer immunotherapy business development head, Ji Li.

Following the recent approval of Genentech's atezolizumab, anti-PD-L1 drugs will add to the flow of new products into IO. There will be enormous commercial competition, which means more clinical trials, trying to generate more data, trying to widen indications, which the big players are doing. IO drugs are already winning approval for more and more indications, and the FDA is still granting breakthrough designations for the new indications. But anti-PD-1 and anti-PD-L1, whether you like it or not, is the backbone, and small biotechs in general today have little choice about using their drugs in combination with that backbone.

HAS OFF-LABEL PRESCRIBING, COMMON WITH CONVENTIONAL CANCER DRUGS, OCCURRED WITH THE IMMUNOTHERAPEUTICS?

Not a lot, because the payers are being typically restrictive about it. As always in oncology, there is a fair amount of it for rich and influential people. It is a horribly unethical mess, the typical result of our strange nonhealthcare system, that poor people are clearly being discriminated against in the most powerful cancer therapy area. Poor people who have cancers that are not in approved buckets for Keytruda or Opdivo are not in general getting treated, unless the therapy is being subsidized at large public teaching hospitals or if the patient can get into a clinical trial for an unapproved indication.

And because of what's happened to co-pays in the last two years, even poor people who do have on-label cancers are often not getting treated with Keytruda or Opdivo. The co-pays for a course of therapy with Opdivo in, say, the approved indication of renal cancer can amount to $18,000. A lot of the people I

ON THE HORIZON: A BISPECIFIC SOLUTION

As noted in our Cancer Immunotherapy Update, industry companies are conducting a very aggressive search for new immunomodulatory targets. But new targets are becoming quite scarce — at least in the more obvious checkpoint inhibitor, PD-1, and co-stimulator realms. As a result, the industry is focusing much more intensely on bispecific technologies where a single molecule or construct can hit more than one target. Many companies are developing a wide range of platforms, from Heat Biologics' whole cancer cells transfected with GP-96 fusion proteins and OX40 ligand fusion protein, to constructed bispecific combination molecule platforms such as BiTe (bispecific T-cell engager) and DART (dual-affinity retargeting), to single antibody bispecifics, including those from Xencor, Shattuck, and Crescendo. Large companies such as Amgen, Novartis, and others are betting heavily on the use of bispecifics in oncology. Preclinical data from some of these technologies shows quite interesting activity when targets such as PD-1, OX40, CTLA-4, and other immunomodulators are combined. Bispecifics are at an early stage, with many unanswered questions, but they are likely to be quite important in immuno-oncology (IO). One of the great advantages of bispecifics, if effective and safe, will be avoidance of "stacking" of IO drug pricing with too many single-target drugs on the market confusing physician choices and reimbursement.

JHL Biotech, Wuhan, China
First KUBio™ Biomanufacturing Solution
May 2016

Transform biomanufacturing

Whether launching a new molecule for the first time, bringing biosimilars to emerging markets, or moving toward commercial manufacturing, GE's Enterprise Solutions provides you with real options at every stage of biomanufacturing. With renewed flexibility, speed and efficiency, we help you extend the availability of quality biologics to regions where they are needed most.

Apply a range of comprehensive solutions including a fully functional facility, flexible single-use platform, integrated automation and a suite of tailored services to accelerate your bioprocessing journey.

gelifesciences.com/enterprise

29215294 AA 07/2016

walked by on the street today don't have $18,000; they never will have $18,000. Are Merck and BMS trying to help? Of course. There are very patient-oriented, ethical, and concerned folks at all of the oncology companies, and they don't like this inequity either. But the very high price of new, truly innovative drugs is creating a serious problem that the industry must pull together to solve.

ARE COMPANIES WORKING TOGETHER TO TEST COMBINATIONS OF IMMUNOTHERAPIES?

Yes, for example, Merck has almost 700 cooperative trials with other companies now underway or in planning in combinations with Keytruda. BMS is beginning to work with companies now. Pfizer is in early stages of creating collaborations and AZ is focusing on a small number of existing collaborations, though their anti-PD-L1 programs likely have less potential for use in combinations than anti-PD-1. Roche is very focused on using its IO platform, including anti-PD-L1, to shore up their aging anti-neovascular and targeted-drug approved therapies.

But the biggest nightmare we will have with combinations is data. Many combination trials are beginning to read out data, and they are all different from one another in patient groups, trial designs, endpoints, error estimators, biomarkers, translations from preclinical data, and dosages. The pharma companies will try to make useful comparisons, but they will almost all be wrong, because the trials are fundamentally statistically different, and comparisons will thus be by definition mathematically flawed. The number of reports we will see in the next year in the financial press, trade press, and scientific press making illegitimate but highly touted comparisons will be truly amazing.

ALTHOUGH WE'VE FOCUSED HERE ON THERAPEUTIC AGENTS SUCH AS ANTI-PD-1, WHAT ARE YOUR THOUGHTS ON THE LATEST DEVELOPMENTS WITH CAR-T?

A number of our original experts have, over time, expressed concerns in meetings and articles about the induction of various T-cell receptors in CAR T cells. Some have felt that the b7 family of receptor ligands might have unknown or untoward toxicity, while the TNFR family would be less likely to have the same risks. Given the recent disaster with the Juno construct, the concern may have been warranted. Although a great deal of fairly complex work will be required to sort out the potential differences, the relative lack of toxicities both in preclinical and clinical use of the anti-TNFR drugs (4-1BB, OX40, GITR, ICOS, TNFRSF25) seems to support the potential difference between the two receptor families. Until the work is done, the ethical issues of using any CAR-T cell preparations in humans should always be questioned, on a patient-by-patient basis.

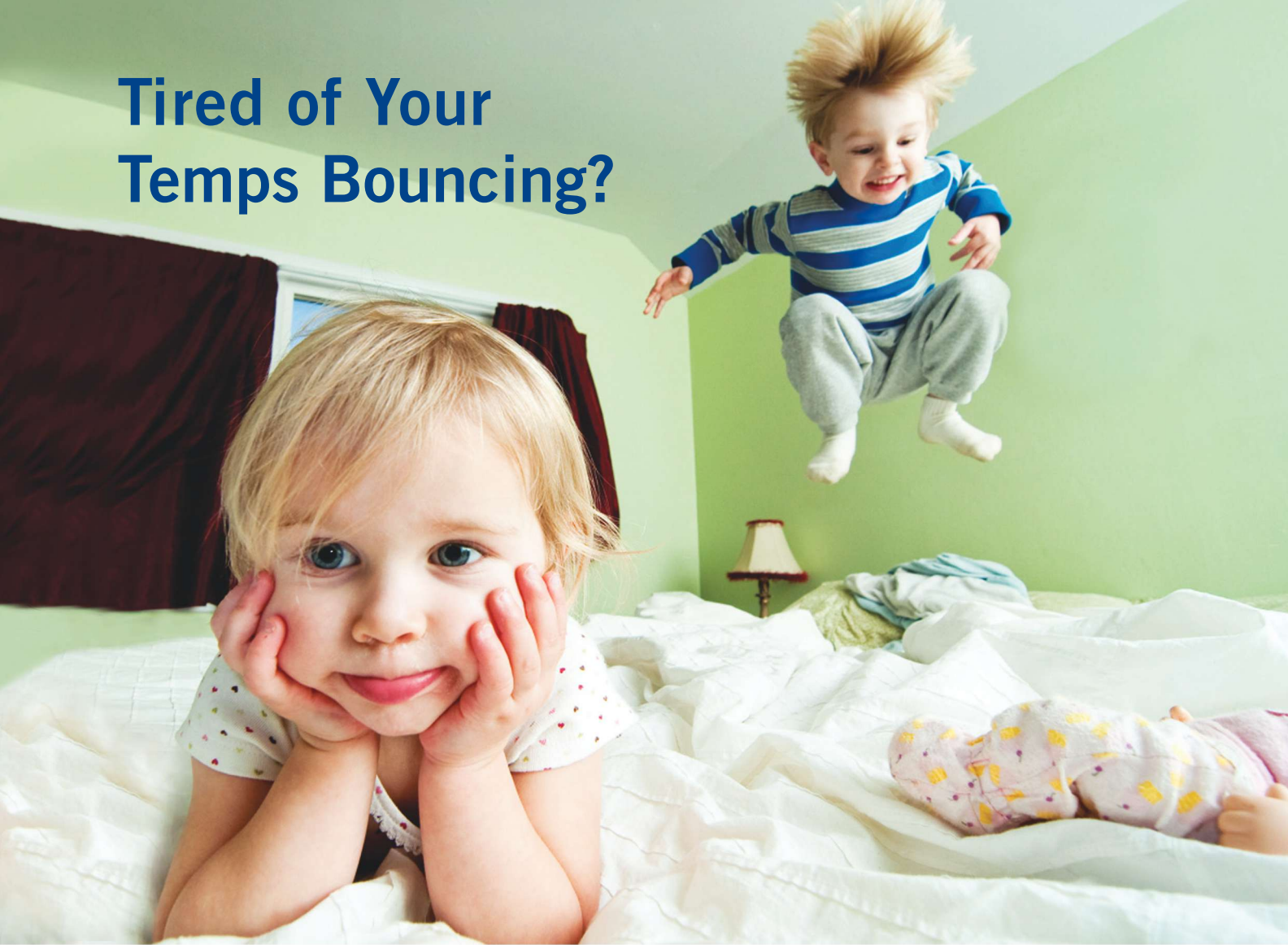
However, perhaps the elephant in the room here is the very large nondrug costs and complexity of administration and patient management with autologous CAR-T. It may be very telling that the large autologous CAR-T players (Novartis, Juno, and Kite) are all looking very hard at allogeneic CAR-T methods that may overcome much of the nondrug cost and complexity questions. Kite's very recent license of the UCLA allogeneic CAR-T patent portfolio is an indicator of this nervousness. Many claim that some of the allogeneic approaches may also address some of the severe toxicity issues, but until human studies are engaged, this is unknown.

EVERYONE'S TALKING ABOUT CRISPR — WAS THERE ANYTHING REPORTED AT THE MAJOR CONFERENCES THAT WOULD INDICATE THE TECHNOLOGY HAS ANY PROMISE IN CANCER?

Nothing actually reported that really says anything. *If* there is a target — such as EGFR (epidermal growth factor receptor) or HER2 — *then* the CRISPR folks will claim all they have to do is change some genetic material and cancer will be cured. But they are even further from proving that claim than gene-therapy proponents are from proving theirs. CRISPR may be very useful for rare metabolic diseases where there is a *deficiency* in a protein. Fix the genes in *some* cells, and maybe they will produce enough of the required protein to reverse the symptoms. Pretty elegant actually. Of course, no one has ever been able to efficiently deliver gene constructs into cells. But, if there is some not-yet-invented way to modify some embryonic cells, and if it is allowed ethically and politically, then it might work in rare diseases.

Dr. Keltner anticipates continuing tumult and change in the IO space in the coming year, and we will continue to cover new developments, as well as prepare for another annual update about this time next year. L

Tired of Your Temps Bouncing?



eurofins | Lancaster Laboratories PSS Insourcing Solutions

Partner and prosper with our award-winning PSS.

Eliminate the ups and downs of continually replacing and retraining temps by retaining our scientists at your site. Hired, trained and managed by us, our award-winning Professional Scientific Services® (PSS):

- Eliminates headcount, co-employment and project management worries
- Avoids Temp turnover rate with managed insourcing
- Costs you less than your own full-time employees
- Delivers a 50-year history of regulatory compliant technical expertise in your lab
- Holds numerous client awards as the top insourcing service provider for the past 10 years

Choose the PSS insourcing solution that enables us to keep staff grounded.

www.EurofinsLancasterLabs.com

LEE JONES
CEO and cofounder of Rebiotix

THE
ENTERPRISERS

Life Science Leadership In Action

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

REBIOTIX: Applying Experience, Finding Adventure

PRIVATE COMPANY

HEADQUARTERS: ROSEVILLE, MN

STARTUP DATE: 2011

NUMBER OF EMPLOYEES: 25

FOCUS: Off-the-shelf, patient-friendly drug-product alternatives to fecal transplant for implanting healthy gut microbiomes.

A straightforward purpose and premise were the words that came to mind in my first impression of this company. Lee Jones, the CEO and cofounder of Rebiotix, describes building the company in an "of course, this is how you do it" manner. The larger issue — whether the company's Microbiota Restoration Therapy (MRT) platform will succeed in a somewhat besieged field — can only be resolved over time. But it will most likely be biology that decides the matter, not the typical lack of clear direction or organization that plagues so many biopharma startups.

As I write this, a Rebiotix rival, Seres, is encountering its own biological challenge, with disappointing mid-term results from a Phase 2 trial of its encapsulated substitute for fecal transplant. The so-called failure by Seres' drug and a few other tentative setbacks with similar competitor products have all the usual pundits with a congenital surplus of confidence rushing to be first to predict the general downfall of microbiome-drug development. As the opinionators accuse developers of excessive claims based on scant evidence, they use the same evidence to rush into a sweeping judgment of the entire space. My guess is that the microbiome field, like any new area of medical promise, will see numerous failures or setbacks before it produces an unqualified success. Thus, in this article, I choose to concentrate on the company-building aspects of Rebiotix rather than conjecture on how its product development will ultimately pan out.

IMPLEMENTING INVENTION

Jones had already put in more than 30 years developing medical products before hitting on the idea of a fecal-transplant replacement in patient-friendly form. (See the sidebar, "School of Enterprise.") Jones and her partners, Michael Berman and Erwin Kelen, founded the company in 2011, all three with a long history in building new businesses. To date, they have raised $30 million in two series, all from private wealthy individuals. Now they are out looking for the company's next round of funding from institutional investors.

Unlike Seres and others, Rebiotix did not try to single out the useful bacteria and separate it from the useless. It took a much simpler approach — collect stool from healthy individuals, process it into safe and stable products, and deliver it in much more tolerable ways than the conventional transplant. The lead product, RBX2660, is delivered by enema; the next in line, RBX7455, by capsule.

"We knew that fecal transplants worked, but people were using them as a technology of last resort because it wasn't industrialized," says Jones. "I was good at doing things like that, and we thought, 'Let's turn this into an industrialized product, figure out what we need to do to make it consistently high quality, stable, and patient-deliverable on demand.' So that's what we did." (See the sidebar, "Put It Where?")

PUT IT WHERE?

Actually, says CEO and cofounder Lee Jones of Rebiotix, the enema form her company is developing with its lead product, RBX2660, is a significant improvement over the fecal transplants it is meant to replace, though its next-generation oral form will be even more patient-friendly.

JONES: We picked the enema delivery for our first product because when we got started, most people were delivering fecal transplants with colonoscopies or nasal gastric tubes. That causes patients a lot of problems, particularly elderly and sick people. We looked through all the literature and found that enemas had the least procedure-related complications and had been done for a number of years. That is how we chose our original formulation. One of our main competitors chose to develop a frozen oral pill as their first product, but we think our enema is a better option because, unlike the frozen pill, the enema may not need a bowel prep. It is like getting a flu shot. Patients go in, get the enema, get up, and go home. Because the bowel prep tends to be the worst part of any procedure, and most people hate that part, we thought patients would be more tolerant to the enema.

We've now finished our Phase 2b multicentered, double-blind, randomized, placebo-controlled trial with RBX2660 in *C. diff* infection, and the results of that will be announced this fall at one of the major medical conferences. We are getting close to starting our Phase 3 trial. Our next product, RBX7455, the oral form, should be entering the clinic in the fourth quarter this year.

A simple idea cannot guarantee a simple execution, of course. "I thought, how hard can this be, the raw material is human stool? But I found out there were no precedents set — no regulatory precedent, and no physical precedent," Jones says. "Nobody even knew how to quantify stool or what was in it, how to strip the microbes out, how to preserve the microbes, because you can't culture them all. It took us more than a year to figure out how to measure, quantify, process, and preserve it."

Rebiotix first approached the FDA in 2012, believing its product would be classified as a tissue transplant. The agency balked, however, because human-resident microbes are not considered human tissue. Instead, the FDA directed the company to submit its product as a biologic-drug product, handled by the Office of Vaccine Research and Review (OVRR) in the Center for Biologics Evaluation and Research (CBER).

Having a clear regulatory track inspired the company to take a longer-term view of its product development. Although Jones and her team believed the enema form would work well as the first generation product, greatly improving on fecal transplants, they would ultimately need to take the patient-friendly concept a step further — to the form of an innocuous, commonplace capsule, devoid of any obvious link to its point of origin. Again, it was a simple idea; its implementation would be an invention in itself.

"I remembered how products like insulin and estrogen got started," recalls Jones. "Estrogen [Premarin] came from mare urine. New treatments often start out with a natural product that maybe isn't so appealing, and then as companies learn more, they can formulate or package the product differently." Its enema product is in Phase-3 development for treating C. difficile (C. diff) infection, which usually requires only a single administration; the capsule product is in earlier-stage development to prevent C. diff. and for prolonged or chronic use to treat conditions such as ulcerative colitis, hepatic encephalopathy, and infection with multidrug resistant organisms (MDRO). The company is developing a separate oral formulation for each of the indications requiring long-term therapy.

Although MDRO infections can occur anywhere in the body, they tend to hide or "colonize" in the colon even after a patient has recovered, making disease recurrence and transmission possible for a long time. Rebiotix has just treated its first patient with an MDRO urinary tract infection in a prospective clinical study at Washington University in St. Louis.

An oral replacement for fecal transplants, though, requires a way to store microbes at room temperature. "We had to invent that, too," says Jones. The microbiota in the gut are anaerobes, so they will die when exposed to air, but in capsule form the microbes cannot be stored in water. "We had to figure out a way to preserve them in a dried format, picking just the right excipients to keep them away from oxygen and water, and then encapsulate them. Today we have achieved more than a nine-month room temperature stability with our oral form, and about two years on the enema form, which is frozen. We have industrialized it so that you can ship and deliver it to patients in a way that fits in with the physician practice."

The company screens donors for disease-causing organisms, based on a list of species maintained and periodically updated according to an agreement with the FDA, but it generally retains the rest of the microbiota regardless of whether every species has a clearly identified role in GI health.

"Our premise was that humans have evolved with a gut microbiome for millennia, and in a healthy person, generally whatever is there works as a community

SCHOOL OF ENTERPRISE

Personal histories of company founders and leaders are more fun in their own words. Rebiotix CEO and cofounder Lee Jones recounts the highlights of her career that schooled her in how to start and run her company.

JONES: I am an engineer by training and also have a business background, and I have spent more than 30 years developing new technologies and introducing them to new markets. I worked for 14 years at Medtronic, and I was involved in multiple startups within that company, including its angioplasty, vascular graph, and InterStim [surgically implanted neurostimulation device for urinary incontinence] programs. Then I left there and ran my own business. I sold that and ended up at the University of Minnesota Office of Technology Commercialization, where I was looking for my next thing to do. They gave me a job in the Diabetes Institute, trying to develop cellular transplant therapies to cure Type 1 diabetes, but we couldn't get that out of the pre-clinical animal stage, so I moved on. Someone in the Office of Technology Commercialization told me about fecal transplants, and I thought, "How stupid of an idea can that possibly be?" So I volunteered to help the university scientists see if it was a viable business.

At that time, it seemed no one knew anything about the microbiome, so I was trying to figure out how fecal transplants would be regulated, because my specialty was taking products from early stage through the clinic and into the market. Then, the scientists got funding and went somewhere else. But I decided that this was such a cool concept, and the more I learned about it, the more excited I got. First, I thought about making a more patient-friendly product that could replace the fecal transplant. I started thinking, "Wait a minute, it's not like rocket science." At least that's what I thought at the time. "I can find my own scientists and do my own work." So I found a partner who had looked at a similar opportunity a year before but couldn't get it funded. The two of us formed a partnership, brought in a third partner who knew financing, and started Rebiotix in 2011.

Grifols Partnership

Better together

PARENTERAL CDMO

Grifols is highly responsive to every customer inquiry for **contract manufacturing** and offers the **agility** and **flexibility** to switch your concentrated formula to **premixed solutions.**

Visit us at the 2016 Contracting and Outsourcing Conference, Table #96
New Brunswick, NJ, 17-18 September

Visit us at CPhI-ICSE, Stand #3J80
Barcelona, Spain, 4-6 October

For more information: Grifols International, S.A.
www.partnership.grifols.com

GRIFOLS

www.grifols.com

to keep the person healthy," Jones says. "So our goal was to replicate as much of that community and keep it as intact as we could. We believe you really can't overdose somebody; the substance is not toxic, so the safety issues are minimal. We've treated more than 300 patients and we have seen no transmission of any kind."

TAKING CAREFUL AIM

The therapeutic targets of Rebiotix have emerged along with scientific advancement in the field since 2011, albeit through a careful weeding and selection of particular indications. From the predominance of C. diff infection as the target of choice, the number of conditions now in testing for microbiome therapy by all companies has expanded to more than 20. "We looked for conditions for which available treatments are inadequate or leave room for a product that isn't the end game — such as ulcerative colitis — where patients begin on a mild medicine, but if that doesn't work, have to go to a very harsh biological."

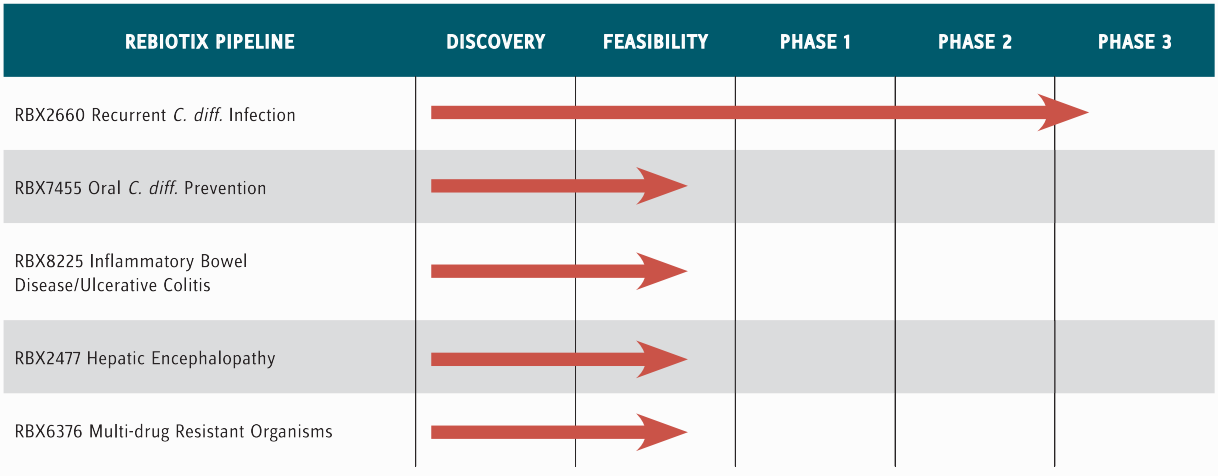
Jones says the company chose indications that offered measurable endpoints "so you weren't left guessing whether or not the product was effective." It also aimed at areas where its products' pricing would raise the least resistance. All in all, she says, the company applied nine criteria to its candidate indications, in consultation with its physician advisory board, to narrow its focus to the five conditions now targeted in its pipeline. Yet serendipity played a role in some cases, as she describes:

"In our C. diff study, we also looked at patients infected with vancomycin-resistant enterococcus (VRE), which causes a severe blood disease if it gets out of the colon. About 40 percent of the C. diff patients were infected with VRE, and we found our treatment could clear the VRE in them as well. We have published clinical data on that."

In a second case, the company got involved with a pediatric gastroenterologist who was interested in testing its MRT approach in pediatric ulcerative colitis, a disease more tractable to treatment at a pediatric level, because it leads to ever greater inflammation over time. "We believe there's a way to stop the cascade of events before the patients get to be adults. So we're doing a trial with a gastroenterologist group in Canada, which had achieved good results in a randomized adult ulcerative-colitis study with their fecal transplants. Now they are using our product in a blinded study for pediatric ulcerative colitis."

SMALL-CAP SPACE

The microbiome is vast. "It is mostly an unexplored universe in its countless species, range of disease-affecting roles, and abundance of possible therapeutic mechanisms and targets. Despite all the hyperbole now circulating over the space, it is still at a stage where



Caution: Drug products are in development and investigational at this time. No product has yet been approved by the U.S Food and Drug Administration.

Rebiotix

the smattering of enterprises operating inside it do not constitute competition so much as confirmation of the microbiome's medical potential. (See "Companies to Watch," *Osel*, April 2016.)

"There are many different kinds of companies looking at the microbiome in many different ways," says Jones. "We're using the microbes themselves as a therapeutic agent. Others are using metabolites from the microbes as a therapeutic option. Some are genetically altering the microbes to improve their effectiveness. This is a new arena for me, but it is also a new arena for almost everyone, which is why I can play here. If it were a pure drug product, I probably wouldn't be qualified, but because it's an open playing field, anyone who's interested can learn. For me, this was a way to get into something I thought would be tremendously interesting. I've met experts all over the world, and they have been my teachers. I tracked them down, brought them onto my advisory board, and learned what was going on."

Out of skillful technological invention, business organization, and therapeutic selection arises the company's straightforward strategy: Anticipate and fill customer needs with patient-friendly products in unserved or underserved therapeutic areas. As the other companies help pioneer the microbiome territory, Jones remains confident in her company's position.

"We're the most clinically advanced of any of the companies that are doing any work with the microbiome, and the first company to take a multi-faceted microbial mix through the FDA. We're about a year ahead of our nearest competitor with a slightly different product."

It's a risky business, drug development, no matter how well you manage it. Yet most people would not want their company to fail because of bad management. We admire the intrepid heroes who jump into the chilly waters of real business without a wet suit. We should also spend some time heralding the people who have achieved sufficient experience, knowledge, and skills in executive management and apply those assets effectively from the point of startup and beyond. L

Driving Innovation In Life Sciences With Agile

NEIL SAWARD AND JUSTINE JOHNSTON

Innovation is a critical capability for life sciences organizations to help them identify and bring new life-saving treatments to patients. According to results from PA's 2015 innovation survey, which includes input from more than 750 senior executives from organizations across multiple industry segments, the life sciences sector is leading the pack when it comes to innovation.

Indeed, the real-world outcomes would also suggest that life sciences organizations are improving their success at bringing new treatments to market. The FDA's Center for Drug Evaluation and Research (CDER) approves hundreds of new drugs each year, and while the majority are variations on previously approved products, a small subset are novel drugs, which are truly innovative products that help advance clinical care. According to the FDA Novel Drugs Summary 2015 (see graph on page 54), the number of novel drug approvals has been slowly increasing over the last decade from 22 in 2006 to more than 40 in both 2014 and 2015.

However, based on industry research, it is clear that even life sciences organizations have room for improvement, and the value of getting innovation right will improve the quality of life for thousands of patients and potentially generate hundreds of millions of dollars in revenue for organizations.

A key first step to help life sciences companies improve their innovation success is understanding the Agile approach and the ways in which life sciences organizations can implement Agile to increase organizational agility and innovation. So what is Agile? It is an approach to implementation, which is rooted in software development. Agile is characterized by iterative design-build-test cycles, scope that changes to reflect changing priorities and frequent delivery of software, rather than the more traditional one-off delivery at the end of a project.

Ultimately, Agile can play an important role in helping life sciences organizations deliver new innovative products to the market faster and in a more cost-effective and streamlined manner. It is an approach that is already being used at some life sciences organizations, and the results speak for themselves. Take, for example, a top five pharma company that recently adopted Agile. After just one year, the switch to Agile resulted in more than $13 million in savings from a small subset of projects, and also enabled a reduction in drug development time scales.

AGILE IS NOT JUST FOR IT

Agile had its origins in software development and quickly proved itself within technology companies as a driver of innovation, quality, and flexibility. As a result, more and more enterprises are now adopting Agile outside of IT to increase organizational agility and innovation. Organizational agility could mean different things to different companies. It could be, for instance, an ambition to increase boundary spanning agility (i.e., the ability to acquire an innovative biotech startup and integrate it rapidly) or to be able to have business model agility (i.e., think budget airlines and their ability to apply differing pricing models rapidly). Despite the differing ways of defining organizational agility, one thing remains clear: Organizations are looking to increase organizational agility to help them release value earlier.

For life sciences companies specifically, opportunities exist for organizational agility across the drug development life cycle by taking a systems view, removing unnecessary complexity, and changing mindsets. Consider this: a top-five pharmaceutical company was developing a non-small cell lung cancer drug, and by using an Agile approach, they were able

Welcome to the

WORKFLOW REVOLUTION

Personalized workflows that lead you to market faster

Every drug takes a different path to market and has its own development requirements. This is why we partner with you to customize workflows to meet your specific needs.

Pharma starts with **You**

Learn more about our solutions for Pharma at bio-rad.com/info/LSL

BIO-RAD

to reach Phase 3 clinical trials in two thirds of the projected time.

PLACING INNOVATION AT THE HEART OF THE ORGANIZATION

Agile is more of a cultural shift than a technical one. Agile's true strength is being able to release the inner energy of teams via the creation of a collaborative culture — one where cross functional teams are given the autonomy to experiment, to continually improve, and to learn from failures. Teams that have fun, autonomy, and purpose are more likely to innovate themselves — a top-down mandate will not achieve the same outcome. Agile techniques, such as retrospectives where teams identify what has worked well, what hasn't, and agree on changes to implement, ensure that teams regularly reflect on how to become more effective.

Technology plays a key role in enabling this culture. As an example, a global pharmaceutical company was able to leverage smarter devices and ways of working to support collaboration. This included the use of smart whiteboards that transmitted in real time to other regions, as well as open rooms with always-on video connections, which allowed them to link up Agile teams across different locations.

LEARNING QUICKLY FROM FAILURE

Failing fast is not a new concept. In fact, actively seeking opportunities where knowledge and skills are stretched to the limit in order to learn quickly is a well-known technique. However, many organizations are still reluctant to endorse failure of any kind. According to the 9th State of Agile Survey, Agile can help translate ideas into reality up to 61 percent cheaper and 24 percent more quickly than more traditional delivery methods, enabling organizations to learn faster and more frugally. Again, some life sciences companies are already benefiting from the implementation of the Agile approach. For example, at a large global pharmaceutical company, this was demonstrated in a program where early experimentation showed that the enterprise-data migration tool would be unable to cope with the forecast data volumes. This early knowledge allowed the company to avoid cost of rework and delays.

HARNESS TECHNOLOGY MORE EFFECTIVELY

Technology is a key enabler of both innovation and bringing treatments to market more quickly. However, too many technology projects still fail to deliver on their goals. Some of the underlying techniques within Agile can help to support more effective deployment of technology, including working in short cycles (known as iterations), early and more frequent engagement with customers, and holding demonstrations at the end of every iteration to show stakeholders progress and to receive feedback.

Together, these techniques all help ensure that the most valuable work is being addressed first, as well as encouraging inspection, adaption, and transparency on a regular basis. Confronting risk early should also be top of mind, with the ambition to significantly reduce a project's risk profile with each iteration.

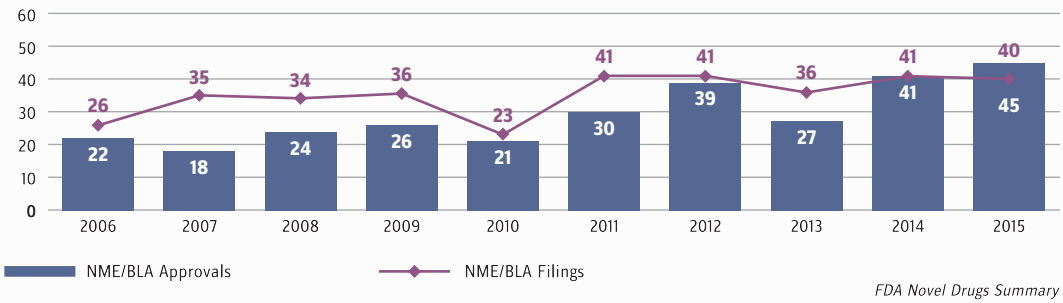
IMPLEMENTING AGILE TO KICK-START INNOVATION

The life sciences industry is complex, due to regulatory changes, new entrants to the industry, and the pressure involved in bringing new drugs to market quickly and efficiently. Implementing the Agile approach can help life sciences organizations innovate to meet these challenges while also reducing costs. In short, companies can see a step-change in their innovation capabilities by adopting and extending Agile beyond IT, moving to an Agile culture, embracing the benefits of failing fast, and digitizing more effectively. L

NEIL SAWARD is a life science expert at PA Consulting Group. He has 20 years of experience covering IT strategy, IT architecture, IT delivery and Agile. He works with senior leaders in the life sciences sector to help them deliver on their strategic IT priorities.

JUSTINE JOHNSTON is an Agile expert at PA Consulting Group, specializing in working in complex technical environments and within large business change and transformation programs. She is a Scaled Agile Framework (SAFe) expert and works to deliver agility, which is value generating and leads to sustainable change.

CDER NEW MOLECULAR ENTITY (NME) AND NEW BIOLOGIC LICENSE APPLICATION (BLA) FILINGS AND APPROVALS



FDA Novel Drugs Summary 2015

alcami®

Connected At Every Level

Alcami is the new CDMO you already know. We connect with our customers intellectually, scientifically and philosophically. Collaboration and a personalized connection on every level, ensure the best possible outcomes for your product. Fully integrated capabilities assist the rapid advancement of your project and mitigate risk. Alcami offers comprehensive pharmaceutical development and commercialization services.

Connect with us.

www.alcaminow.com

Visit us at CPhI booth #3H51
and AAPS booth #303.

AAIPharma Services and Cambridge Major Laboratories are now Alcami.

The Common Elements Of Top-Performing Pharmas

GAIL DUTTON Contributing Writer @GailLDutton

Top-performing pharmaceutical companies aren't like their peers. The top six companies have each found their own "secret sauce" that, according to a recent Accenture report, helps them dominate their markets and boost profit margins far beyond those of their peers.

For the top performers — Novo Nordisk, Bristol-Myers Squibb (BMS), Astellas, Amgen, Roche, and Eli Lilly (in order) — "business as usual" was transformed a decade ago when the industry recognized the looming patent cliff. Each of the top six companies developed its own formula for success, but they share some commonalities that have created a significant performance gap between themselves and all the others.

According to Accenture's "High Performance Business Review," the top six performers each:

- focus their pipelines to maximize R&D productivity
- use collaboration, mergers, and acquisitions to dominate their target disease areas
- develop new, agile business models to respond to dynamic market conditions (including the new pressures of affordability and healthcare consumerization)
- excel at product launches by mastering flexible pricing and market access to produce superior outcomes.

MAKE GUTSY DECISIONS

Finding the "secret sauce" that enables success requires balancing focus with breadth of research. "It is about deciding what areas you want to play in, and playing to win," says Paul Biondi, head of business development at Bristol-Myers Squibb. "Finding that balance isn't easy. It takes a lot of gutsy decisions."

BMS has made several "gutsy" decisions. In 2007, it began transforming itself into a biopharma company. That meant divesting its nonpharma businesses to focus on biologics and innovative medicines for serious diseases. More recently, it divested its diabetes business and early virology pipeline to concentrate on immuno-oncology.

"We had great success in diabetes and virology, but we realized future advances would be incremental compared to the opportunity to transform the way cancer and other diseases are treated," says Carl Decicco, Ph.D., head of discovery, BMS. Not coincidentally, this was an area in which the company already had expertise.

One of the strategies BMS uses is based on leveraging its extensive knowledge base to transcend programs and thus help researchers uncover synergies and build upon existing data to streamline development. For example, its immunoscience research accelerates its immuno-oncology work.

Woven into each of its decisions was the determination to build a carefully focused pipeline. "A key differentiator at Bristol-Myers Squibb is the equal balance between internal and external innovation, which is mutually connected to building and evolving our portfolio over time," Decicco says.

FOCUS RELENTLESSLY ON INNOVATION

When Lilly faced the patent cliff, it consciously went against analysts' advice. "We made the decision several years ago not to get into specialty pharma or generics (as analysts advised), but instead to focus relentlessly on innovation," says Darren Carroll, SVP, corporate business development. "We doubled-down and ensured we had a pipeline of innovation to meet unmet medical needs."

The 70-plus agents in its pipeline today are concentrated around diabetes, oncology, immunological diseases, neuroscience and pain, and cardiovascular disease. Two of those, diabetes and oncology, were chosen because of longstanding success in those areas. The others resulted from collaborations or acquisitions. For example, in 2008, Lilly acquired the biotech

eppendorf

We Know Bioprocessing

Eppendorf bioprocess solutions—for all your bioprocess needs

The Eppendorf bioprocess portfolio combines the DASGIP and New Brunswick product lines to offer a complete portfolio of scalable hardware and software solutions for R&D, process development, pilot and production.

- > 35 mL to 2,400 L working volumes
- > Parallel Benchtop Bioreactor Systems
- > Autoclavable and SIP fermentors
- > Rigid wall single-use vessels with 65 mL to 40 L working volume
- > Precise and intuitive process control
- > Comprehensive information management

www.eppendorf.com • 800-645-3050

company ImClone, gaining the cancer therapy Erbitux (a monoclonal therapy that inhibits epidermal growth factor receptor inhibitor) and research facilities in New York City. Through collaborations, Lilly acquired new molecules that pivoted its central nervous system program from neuropsychiatric drugs to neurodegenerative medicine. Its autoimmune programs were developed through partnerships and its internal work with IL-17, which has blockbuster potential as a psoriasis treatment.

Lilly changed its business models too, sourcing innovation throughout the world. "We pioneered investment in alliance management across the industry to help ensure we get the value early on," Carroll says. That includes substantial investments and innovation sourcing in Asia, which has led to new medical entities for autoimmunity.

The formation of Lilly Asia Ventures — "the first VC firm of its kind in the industry," Carroll says — enabled Lilly to better understand the global risk capital market, which led, in turn, to project-focused investing. "With our fund manager partners, we created new funds that invest in single molecule companies. Almost every penny of investment is focused on developing molecules, rather than building labs or hiring the right CFO." Consequently, the resulting companies are built to sell.

That idea evolved from an autonomous Lilly division called Chorus. "Chorus' elite developers have a fast, lean approach to clinical proof of concept for candidate stage molecules through Phase 2A. Part of our approach to venture capital is making Chorus developers available to companies created by our venture partners, so the developers function like extensions of the company," Carroll explains.

Lilly has created 14 companies using the Lilly VC model. "This approach ensures their innovation meets our standards. It's already paying dividends in terms of financial returns and bringing new molecules into the pipeline. And," he adds, "this model generates a profit."

That type of collaboration is ideal for small biotechs, but unnecessary for big pharma peers. Consequently, collaborations among peers (including Pfizer, Boehringer Ingelheim, and AstraZeneca) leverage mutual capabilities and share big risks. Lilly's first such collaboration was with Boehringer Ingelheim to develop Tradjenta (linagliptin). In July 2016, the two announced a clinical trial collaboration in metastatic breast cancer.

EMBRACE A NEW VISION

Astellas, in 2005, created a development road map that called for the relentless pursuit of new science in the areas of urology, transplantation, and oncology, says Bernhardt "Bernie" Zeiher, president of development at Astellas. "The 2015 iteration of that plan calls for evolving our business beyond our existing therapeutic areas and into muscle disease, ophthalmology, regenerative medicine, and next-generation vaccines." One year into that plan, Astellas is collaborating with others in the areas of immuno-oncology and muscle disease and building internal expertise in regenerative medicine and DNA-based vaccines.

While resetting its vision, Astellas also integrated scientific and medical functions within the organization. Now development, medical affairs, pharmacovigilance, clinical and research quality assurance, and regulatory affairs report to the chief medical officer. "This enhances creativity and helps us anticipate and address evolving challenges, discoveries, opportunities, and expectations in the global healthcare system," Zeiher explains.

Importantly, information learned during various programs is leveraged across conditions with similar biologies or mechanisms of action to take advantage of synergies and to expand into adjacent diseases. "For example, leveraging our expertise in transplantation and infectious diseases, Astellas is developing the world's first DNA vaccine for cytomegalovirus (CMV) infections," Zeiher says. ASP0113 is in clinical trials for immunocompromised individuals undergoing medical procedures who are at risk of reactivating the virus.

FINANCIALS SHOW POLARIZING DIFFERENCES

The difficult decisions made by Astellas, Lilly, and Bristol-Myers Squibb made them top performers. "There are a number of key characteristics distinguishing the top performers," says Anne O'Riordan, global senior managing director for life sciences at Accenture. A quick analysis of the financials proves her point.

Top performers have a CAGR of 5.3 percent, versus 2.9 percent for all others. Likewise, operation margins for the top six performers were 28.9 percent, compared to 18.1 percent for all others. She attributes these differences to top performers' abilities to "get the right products to market at the right time.

"The pipeline replacement strengths of the top six companies are significantly higher than those of the rest of the industry," O'Riordan says. Accenture predicts recent and upcoming launch growth will constitute 40.7 percent of sales 2015 through 2019 (estimated). For other companies, the average is 23.5 percent. Measured another way, top performers are poised to replace each dollar lost to off-patent drugs with $4.30 in sales of new compounds (before profitability adjustment). For the rest of the industry, that figure is $1.60.

"High performers tend to externalize R&D," O'Riordan says. External projects' forecast growth 2014-20 for top performers represented 55.3 percent of 2014 revenues, versus 45.7 percent of the growth of all others. The CAGR for external products was 5.6 percent for high performers, versus 2 percent for the rest. That creates a symbiotic environment for small biotechs.

"The large companies can complement the skills of smaller companies and bring much deeper knowledge of global markets and established sales forces. When brought together, the result can be magical."

WILL PRICING PRESSURE TOPPLE THE LEADERS?

To continue to outperform the industry, these six companies must continue to adapt to disruptive change in the industry. For example, Accenture reports a $50 billion shortfall loom between analysts' 2015-2020 sales forecasts for recent and upcoming launches and the additional funds payers in developed markets are expected to have available. With $258 billion in new launch sales forecast, and only $208 billion available to payers, companies must find innovative ways to close that gap.

That shortfall likely will be exacerbated by shifts to outcomes-based reimbursement. "Novartis and Amgen, for example, are signing on for outcomes-based payment to reduce total healthcare costs," O'Riordan says.

The wide availability of highly effective generics and biosimilars increases pricing pressures. Because many extremely effective products have gone off patent, payers today have more choices among generics. To be listed on payers' drug formularies, these top companies had to develop new classes of therapeutics that were more effective and deliver better outcomes for patients and healthcare systems.

Innovative science, however, is no assurance of commercial success. In 2015, despite more drug approvals than any year since 1996, innovative medicines were largely inaccessible to patients because they weren't included on payers' drug formularies. Between 2011 and 2013, the proportion of new drugs accessible to patients fell 9.5 percent, according to Accenture. That reality, highlighted by Gilead's experience with Sovaldi (which often cures hepatitis C but was kept off formularies because of its expense), caused the industry to rethink market access in terms of meeting the medical needs of patients as well as the economic needs of payers.

At Astellas, rethinking market access involves working with payers, providers, and patients early in the R&D process to drive value by understanding patients' needs as well as those of today's integrated healthcare systems, Zeiher says. Astellas' partnership with Humana is designed to improve patients' experiences by reducing inefficiencies in managing oncology, urology, and immunology.

For top-performing companies to maintain their high performance, they must continue to keep pace with both market and scientific innovation. Having an amazing molecule and meaningful product differentiation are vital, but those are only part of the requirement. Companies must be able to deliver a continuous stream of innovation that addresses the medical and economic needs of their markets in a dynamic healthcare economy and thereby meet sales targets that drive high margins. L

Is Your Board Capable Of Overseeing IT?

GAIL DUTTON Contributing Writer @GailLDutton

Life sciences companies are at a crossroads, although they may not recognize it. Information technology is transitioning from a tool to a strategic element that contributes to business success. Most boards, however, are ill-equipped to guide this transformation.

"There's an interesting dynamic now in which technology is permeating every aspect of organizations," says Patricia Lenkov, president, Agility Executive Search. "Every company, including biopharma, has an opportunity to leverage IT strategically. IT people feel boards don't really understand that."

They're not wrong. Multiple studies indicate board members want more information but, trained in finance or science, often don't know what to ask to ensure satisfactory oversight. To compound the challenge, the average age of board members is just over 63, according to the 2016, multi-industry PwC study, "Directors and IT." This means many entered the workforce when slide rules were more common than calculators, and computers meant mainframes. PwC concludes, "This means many directors are uncomfortable overseeing their company's IT."

Less than one-third of the 800 PwC study respondents were confident their companies' approaches to IT provided the board with adequate information to manage IT risks and opportunities. Board members clearly want to better comprehend the risks and opportunities related to IT. To do that, someone on the board should have more than merely a basic understanding of how IT is used in the company and how it can be used to capture opportunities.

"It is impossible for all board members to have a granular understanding of IT architecture and design, but members should have sufficient knowledge to fulfill their fiduciary duties," says Richard A. Brand, CFO, BeyondSpring Pharmaceuticals, a clinical stage biopharmaceutical company.

WHAT BOARDS DON'T UNDERSTAND

One of the most common IT misperceptions among board members, according to the PwC report, is a belief among more than two-thirds of respondents that their company's web and mobile applications are assessed for potential threats before being deployed. In reality, IDG Research reports that 62 percent of applications are never checked for vulnerabilities before deployment.

Another misperception, Lenkov says, is the belief that technology can be discussed separately from the business – that it's not strategic and can be siloed. In reality, IT handles more than email and data storage. Today, it is integrated throughout organizations, affecting operations, competitive intelligence, marketing, logistics, and every other function.

Also, Lenkov adds, "Board members don't know what they don't know." This often becomes evident when discussing cybersecurity. After major cyber breaches at Home Depot and Target a few years ago, boards began to realize that all companies and all industries are vulnerable to cyberattack, but they didn't understand how or why their own companies were vulnerable. In the case of Home Depot and Target, the attacks were launched through air handling equipment's SCADA [supervisory control and data acquisition] systems, which were assumed to be irrelevant to IT security.

One way to minimize such misperceptions is to allocate a board position to someone who can ask the right questions and also understand the answers and their implications. In this way, board oversight of the organization's IT operations may be assured.

WHAT THE BOARD SHOULD KNOW ABOUT IT

IT involves far more than it did even five years ago. Rather than just ensuring data integrity, storage, and communications, new technologies are coming online that support accurate, near-real-time data acquisition and digital health initiatives that bring drug developers closer to patients. As IT investments become more strategic, governing boards need to understand them.

Overseeing IT at the board level doesn't require granular expertise, but it does imply more than cursory knowledge. Instead, "Boards need some modicum of awareness of the facility and the possibilities, the willingness to include IT in a budget, and knowledge of competitive pricing for IT elements," says James Manuso, Ph.D., president, CEO, and vice chairman of the board of directors, RespireRx Pharmaceuticals. "As a board member, you're asked to improve budgets, but if you don't appreciate the importance of protective measures both intra- and extracorporately, you may

WWW.CAPSUGEL.COM

ENGINEERING MEDICINES TO LIFE

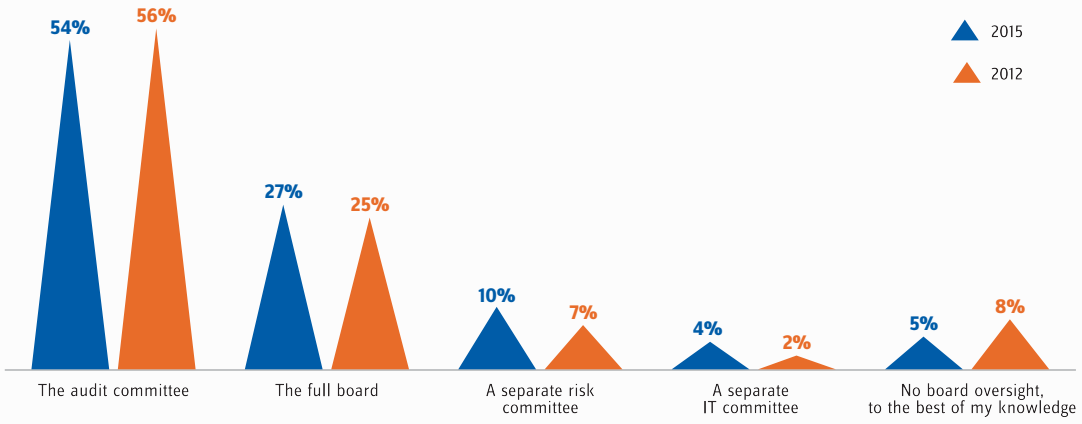
Capsugel®

RISING TO THE CHALLENGE

Tomorrow's complex medicines face challenges to overcome low bioavailability and optimize drug delivery. This calls for a partner with the credibility, ingenuity and flexibility to deliver both the product and process design required to make your compound a commercial reality. With a unique range of technology and integrated product development from design to commercialization, Capsugel is that partner.

VISIT US AT CPhI AT BOOTH 3R16 & AAPS AT BOOTH 1101

WHO ON THE BOARD CURRENTLY HAS PRIMARY RESPONSIBILITY FOR THE OVERSIGHT OF IT RISKS?



Source: PwC

see those measures as unnecessary or unimportant."

Brand explains that a board should determine whether cybersecurity insurance coverage is needed to protect the company financially if an IT breach occurs, regardless of whether that breach affects clinical operations or other strategic, management, and financial activities, and whether strong safeguards are in place. Boards also should be concerned with how electronic information is maintained and what steps have been taken by management to ensure a smooth transition to back up operations when an IT service interruption has occurred.

"To fulfill its fiduciary responsibility, a board needs to perform due diligence on third-party service providers on an ongoing basis," Brand continues. "This includes obtaining annual compliance reports from the provider regarding the systems, controls, and responsibilities of that organization." Some concerns may include whether the IT provider has, and exercises, a business continuity plan, and whether it is in compliance with relevant regulatory agencies regarding data protection and patient privacy. While the board should ask such questions, someone on the board also should be able to evaluate the details of the responses.

In addition to some familiarity with cybersecurity and liability for breaches, board members should also appreciate the evolving, increasingly strategic opportunities IT offers for strengthening corporate intelligence, sales, and other areas. This necessitates some familiarity with the relative merits of various platforms (such as virtual computing or public versus private clouds), the opportunity costs of maintaining legacy systems, as well as the knowledge to assess the true cost of various vendors. (For example, some vendors own the database your data populates, hampering your ability to change vendors because without that database, the data is unstructured. This is called vendor lock-in.) Benchmarking IT spending compared to competitors also may provide valuable insights.

IS ON-BOARD INSIGHT A DISTRACTION?

Boards typically address such concerns through presentations by vendors, consultants, and in-house IT specialists. "Many boards feel they understand as much as they need to through occasional briefings," Lenkov says. That reliance on external expertise negates real oversight, however. It is the equivalent of reading a financial report without the expertise to interpret it.

Manuso disagrees, saying, "Actually having IT expertise on the board is pushing the envelope unless that person also has extra expertise that's of unique value." IT expertise may be valuable on the board, he says, if the company relies heavily on next-generation computing systems that advance competitiveness or that expertise is critical for strategic, operational, or financial decisions. That's not yet common with pharma, although Big Data, predictive analytics, and digital healthcare may change that.

Particularly before commercialization, companies may be better off filling the board with experts to guide them through clinical trials and regulatory hurdles. "As long as the executive team has granular IT awareness," Manuso says, "filling a precious board seat with an IT expert may be a distraction."

That changes when the company develops an external sales and marketing strategy. At that point, the lack of IT expertise on the governing board may compromise directors' ability to exercise adequate oversight.

Vertex Pharmaceuticals, with R&D and commercial offices on three continents, added IBM executive and global IT thought leader Yuchun Lee to its board in 2012 to provide that oversight. As Jeffrey Leiden, M.D., Ph.D., chair, president and CEO, said at Lee's appointment, "Companies must provide both reliable real-time

information and innovative products." By appointing Lee to the board, Vertex can do both.

WHAT TYPE OF EXPERTISE IS BEST?

"Although technical presentations should be at a level all directors can understand, having a true expert on the board to grasp implications that aren't obvious to those not in the field can be very beneficial," Lenkov insists. Likely candidates include executives from technology companies, as well as the CIO or chief technology officer.

The type of technology expert matters. "A technology CEO understands how technology can be harnessed to push the company forward to reach its goals," Lenkov points out. This executive is likely to understand industry best practices and broad challenges for a range of technology solutions. Current industry knowledge is imperative. Therefore, even recently retired executives are likely to be outdated.

The company CIO or CTO is an alternative to placing a technology company executive on the board of directors. These executives understand technologies and their interdependencies at a deep functional level.

"Today's CIO and CTOs are strategists. They make big technological decisions and understand, tactically, what technology can do for a company," Lenkov says. CIOs would point out that they run businesses within business and, like the CFO, are partners in strategy development. The downside, however, is that this executive is asked, essentially, to oversee him- or herself.

TECHNOLOGY COMMITTEES ARE EMERGING

Typically, the board's audit committee oversees IT, according to the PwC study. As companies realize the critical nature of technology, some are creating a separate committee specifically for technology. This implies the shifting of IT concerns from risk – a main audit committee issue – to opportunity.

"Technology committees aren't overly common," PwC analyst Barbara Berlin notes. Overall, only 4 percent of boards in the PwC study had technology committees. Among pharmaceutical and biotech companies, only a few (including Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Pfizer, and Teva Pharmaceuticals) have established science and technology committees to provide strategic advice on the company's direction regarding technology and R&D and their implications for the organization. In other industries, board-level technology committees also exist at Novell, Procter & Gamble, FedEx, and JP Morgan. They are only slightly more prevalent than boards that include IT expertise.

Information technology is beginning to confer a competitive advantage. Depending on their stage of development, life sciences companies should consider the relative merits of having one board member well-versed in new and emerging opportunities that technology makes feasible.

For clinical-stage companies, board-level IT expertise may be a distraction. For large pharmas, however, it may be a necessity, providing the blend of business and technical insights that helps forward-thinking companies leapfrog peers and gain market share.

The Increasing Importance Of Real-World Evidence In Drug Development

SUZANNE ELVIDGE Contributing Writer @SuzanneWriter

Market access is all about getting the right drugs to the right patients at the right time and for the right price. But to do so, every pharma or biotech company must face a mounting set of challenges, including, most prominently, high research costs and tighter budgets.

That's why a formalized and optimized market access strategy is essential these days. One of the most important components of that strategy (i.e., plan) is real-world evidence that reflects how patients use and benefit from drugs in an everyday setting.

GENERATING AND ANALYZING REAL-WORLD EVIDENCE

Real-world data is increasingly demanded by payers, providers, and health technology assessment (HTA) bodies as a reflection of a drug's cost-effectiveness. This raw data is collected when drugs are used in a real-world setting outside the constraints of standard clinical trials. It can be generated from a variety of sources, including patients' electronic medical records, wearable sensors, devices and apps designed to support disease management, and patient-reported outcomes (PROs). Another source of real-world data is from discussions between patients on social media. Real-world data on drug efficacy, safety, and everyday use is available from Phase 4 studies, retrospective studies, or analysis of data in registries. Compiling and analyzing all of this data creates a package of usable and relevant real-world evidence that is much more patient-centric than data from randomized controlled trials (RCTs).

BUILDING BETTER CLINICAL TRIALS

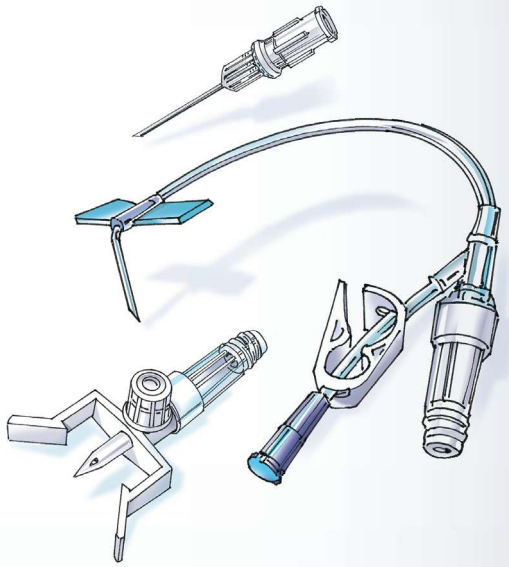
RCTs are used to assess the safety and efficacy of new drugs under standardized conditions, enrolling only people who fit within strict criteria of age, severity of disease, gender, and even body mass index (BMI). This narrow set of criteria can mean that drugs appear to perform better or worse than in everyday use, according to Raf de Wilde, who is a global pricing and market access expert at Valid Insight, a global provider of strategic market access consulting and evidence development services. He cites NOACs (novel oral anticoagulants) as an example. In clinical trials, it was difficult to show better efficacy for NOACs compared with Warfarin (a blood thinner) in preventing strokes associated with atrial fibrillation. However, in everyday use, NOACs were more effective as patients are more likely to stick with NOACs than Warfarin treatment. In contrast, some drugs can perform more poorly in the real world, as the patients may not fit the RCT criteria – they may be older or younger, be at a more advanced stage of disease, or have comorbid conditions for which they are taking other medications.

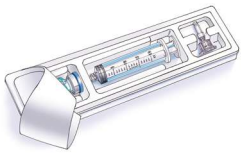
As the costs of developing innovative drugs climb and drug budgets are under the joint pressures of changing patient demographics and funding cuts, payers are becoming more cautious about believing the data from clinical trials, particularly for new and high-cost drugs. Instead, payers are increasingly looking for real-world evidence of a drug's cost-effectiveness, either by reducing the costs of disease management or improving patient outcomes. Usually, real-world evidence isn't available until after a drug is launched, but there are ways to get real-world-type data in clinical trials, for example, by using observational pragmatic studies. These studies enroll patients who are more like the general population (i.e., closer to routine clinical practice) and compare the new drug

B BRAUN
SHARING EXPERTISE

These things make life convenient.

These things make your drug convenient.





Bundle your drug with devices to make administration convenient.

Caregivers have demanding jobs. What if you could help them work smarter by making your drug quick and easy to administer? B. Braun's OEM Division can create a customized bundle of all the devices needed to administer your drug. It'll make your drug convenient for caregivers and separate you from competitors. We offer an extensive selection of proven devices plus design, regulatory, lab services, packaging and sterilization expertise. It's a full suite of capabilities designed to give your drug even more benefits.

B. Braun Medical | OEM Division | USA | www.bbraunoem.com

with existing treatments rather than a placebo.

Real-world evidence plays a role early in drug development, where understanding the current and future market landscape is important for therapeutic area and lead candidate selection. It can affect the design of clinical trials, for example, by highlighting the endpoints that will be of most relevance to patients and physicians (e.g., focusing on abilities useful to daily living rather than timed walking tests in neurodegenerative disease). By understanding the size and location of patient populations, real-world evidence also can help when recruiting for clinical trials. This is especially important for studies of drugs for rare diseases or disease subtypes, where companies struggle to recruit from a small patient population.

CREATING A POWERFUL VALUE STORY FOR PAYERS AND REGULATORS

To gain the best possible market access outcomes, pharma companies can use real-world evidence to build effective and compelling value stories. As well as clinical data, these stories should include population size, disease burden and unmet need, drugs in the pipeline, and the effectiveness and cost of competitors. In addition, to optimize market access, companies need to think about the needs of payers and regulators.

Payers may distrust data from pharma companies, and as a result, are beginning to collate their own real-world evidence, seeing it as more relevant than clinical trials data or data produced by pharma companies, says de Wilde. One example includes the use of MUR (medicines use review) data to understand how patients are using drugs, such as how often they are refilling prescriptions. KCE, the Belgian health technology assessment body, is capturing and using real-world data, such as how persistent patients are in taking their Alzheimer's disease drugs. Healthcare plans in the U.S. are also using real-world evidence when looking at the impact of different drugs on costs. As de Wilde adds, if the industry doesn't produce real-world evidence, its key stakeholders will. Finally, drug-value stories based on real-world evidence can help physicians decide which drug to prescribe since the physician can see the outcomes from patients with similar profiles. These stories can also help physicians educate patients about the side effects that they might expect, what they can do to manage the side effects and improve their quality of life, and when to alert healthcare professionals about serious side effects.

GAINING EARLIER APPROVAL THROUGH REAL-WORLD EVIDENCE

There are a number of initiatives designed to accelerate drug approval, and therefore, earlier access to drugs, that rely on follow-up real-world data collection. "The real-world data generated through accelerated pathways may provide answers to payers' questions about how the drugs are used in real day-to-day clinical practice," says Steve Bradshaw, managing director of Valid Insight.

"It's important not to underestimate how far real-world evidence can take us in the overall mission to improve health outcomes and to achieve commercial success."

STEVE BRADSHAW
Managing Director, Valid Insight

The European Union has a number of accelerated approval processes in place, including conditional marketing authorization and an adaptive pathways process. Conditional marketing authorization allows early approval based on interim data for drugs that target seriously debilitating or life-threatening disorders, rare diseases with orphan designation, or emergency health situations. Companies have to commit to collecting real-world data or continuing clinical trials to support full approval. The adaptive pathways process allows patients and physicians to access drugs pre-approval based on data from a small group of patients or by using a surrogate endpoint. Again, the company has to continue to collect real-world data to support full approval.

The U.K. has an Early Access to Medicines Scheme (EAMS), which also allows seriously ill patients with major unmet needs and no other options to access drugs pre-approval (potentially as early as the end of Phase 2 trials). Japan is putting together its sakigake (pioneer) strategy to allow conditional approval for regenerative medicines, with full approval allowed based on real-world evidence. The U.S.'s accelerated approval process allows drugs to gain early approval based on surrogate markers or intermediate clinical endpoints, followed with Phase 4 confirmatory trials for full approval.

Of course, there are still challenges associated with drugs that are approved using these accelerated pathways. In some countries the drugs are paid for by the pharma companies, but in others, the funding

comes from the health providers. In the latter case, some payers, according to de Wilde, may still feel there isn't sufficient data and will want to wait until the full evidence is available on the efficacy and cost-effectiveness.

EXTENDING THE LIFE CYCLE AND GETTING NEW INDICATIONS

Many companies just focus on market access and real-world evidence when planning to launch a new drug. But Bradshaw says, "A market access strategy isn't just about planning for launch; it's about how we can gain and sustain market access through to patent expiry and beyond. It's important not to underestimate how far real-world evidence can take us in the overall mission to improve health outcomes and to achieve commercial success. We see real-world evidence being particularly useful to substantiate incremental value, especially where the benefits might be impossible to determine through a standard clinical development program."

Real-world evidence also can help maintain brand loyalty by affirming the safety, efficacy, and cost-effectiveness of a drug in everyday use. It can build trust between healthcare professionals and pharma companies and prolong the life cycle of a drug, even once generics reach the market. Real-world evidence based on data collected from patients — for example, using wearables or technology-enabled delivery devices — can be used to confirm the proper use of a drug to physicians and report its correct use to payers.

As an example, De Wilde cites the development of easypod by Merck Serono and PDD, an electronic injector for Merck's recombinant human growth hormone, Saizen. As well as making administration easier for patients, the easypod records how much drug is administered and how often, which could be valuable information to physicians and help detect any misuse of the device to increase muscle size. De Wilde adds that companies could use this kind of technology to support market access by saying, "We believe our system will ensure that patients will manage their treatment better and for longer, or we will give you your money back."

LOOKING TO THE FUTURE

There are still a number of challenges that need to be resolved. The collection and analysis of real-world data can currently be costlier than data generation through RCTs. However, advances in technology and support through collaboration may help to resolve this in the future. Data privacy also remains a stumbling block, as medical data is very personal. On a larger scale, current regulations limit data sharing between Europe and the US.

By working on the challenges and making the most of the opportunities, real-world evidence has potential to be a powerful part of a market access strategy, from clinical trials to approval and beyond.

Great Expectations For Personalized Medicine Outside Oncology

PETER KEELING AND STEVE VITALE

Oncology has always been the front runner in personalized medicine, so this is where targeted therapies and diagnostics have, for the most part, been focused. However, there is new activity outside this area where biomarker and targeted approaches are proving successful.

There are now biomarker-driven therapies for diabetes and inflammatory diseases and neurological diseases. The number of targeted drugs in this space has doubled in five years, and while oncology still dominates as the single most important therapy area, development in other disease areas has increased exponentially.

Outside of oncology, there will be multiple entry points for biomarkers that are not necessarily blood-based. Depending on the disease area, new diagnostic tools such as wearables can be employed singly or in combination, making the non-oncology space a more complicated but competitive landscape. These tools may ultimately be employed to differentiate certain brands, drive faster regulatory approval, and/or improve the value proposition presented to payers and patients.

IS THE FUTURE ALREADY HERE?

Pharma is already gearing up for a non-oncology future, as demonstrated by a sharp increase in personalized medicine deals outside of oncology since 2011. Deals between pharma and diagnostic or lab partners have started to converge in both spaces. As such, non-oncology could be equally, if not more, active as oncology. But there could be a change in the volume and nature of the agreements that pharma has with external partners in this space. Additionally, the focus of such agreements, which is towards technology partnering, may change, as shown by Novartis and Microsoft teaming up to further develop Kinect for MS assessment.

A DIVERSE TESTING LANDSCAPE OUTSIDE ONCOLOGY

In MS, the gold standard for diagnosis is imaging, but there is significant work being done on biomarkers to identify patients, or measure therapeutic response to pharmaceutical interventions. Stratify JCV was developed to address a significant safety issue for a specific therapy, but many companies are trying to identify a prognosis biomarker to identify and track disease progression. In addition, sensitive wearable technologies can gather data on daily movement and motion to inform the clinical perspective. Clinical trials reveal substantial activity in this area, while health apps and devices are expanding from the consumer field into the diagnostic world.

We also can expect to see a rise in the use of diagnostics at opportune points early on the treatment pathway. In rheumatoid arthritis, for example, big issues restrict biologics to a small patient pool in the very late stages of the disease, when damage to the joints has already been done. But research shows that earlier identification and treatment can reduce joint damage and improve quality of life. By identifying inflection points on the pathway, and incorporating existing and novel biomarkers, is it possible to create a perfect storm of diagnostic, education, and novel therapy to get earlier treatment to the right patients that also benefits cost-management? Collaboration with payers on this last point could provide the incentive to make sure tests are used as early as possible and have rapid uptake.

NON-ONCOLOGY PERSONALIZED MEDICINE

The non-oncology space may be complex and risky, but it offers significant benefits. It is likely pharma companies will create diagnostic entries into treatment pathways where they hold valuable assets. This could impact product uptake, peak sales, access, and pricing discussions, because there is a strong correlation between the choice of test, particularly early in the treatment pathway, and the potential to avoid costly outcomes later.

Competitors in key disease areas are lining up some interesting multitest strategies. As a result, "one-size-fits-all" therapies will increasingly be competing with test-enabled therapies, and 2017 will be a key tipping point. L

PETER KEELING is CEO and **STEVE VITALE** is managing director of Diaceutics Group, a dedicated integrator in the personalized or precision medicine space.

American Airlines Cargo

With you all the way.

Our goal is to see things from your perspective and anticipate your every need – especially when it involves incredibly sensitive shipments. With a larger, expanding network, we're coming together to provide a global cold chain solution that ensures on-time, uninterrupted, temperature-controlled delivery, even in hard-to-reach locations.

ExpediteTC°

Learn more about Expedite TC°℠ at aacargo.com/expediteTC

How To Be A Three-Box Leader

VIJAY GOVINDARAJAN

VIJAY GOVINDARAJAN is the Coxe Distinguished Professor at Dartmouth's Tuck School of Business and a Marvin Bower Fellow at Harvard Business School. He is the author of *Three Box Solution: A Strategy for Leading Innovation*, HBR Press.

In a nutshell, the *Three-Box Solution* describes the framework for managing a business's responsibility to take action in three time horizons at once: executing the present core business at peak efficiency (Box 1); taking steps to avoid the inhibiting traps of past success (Box 2); and innovating a future built on nonlinear ideas (Box 3). Leaders must understand the distinctive skills each box requires, how the boxes interrelate, and what it takes to balance them.

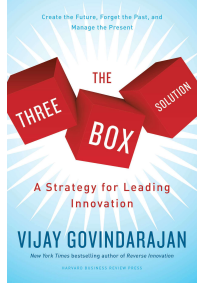
We now live in an era of almost constant change. First, new technologies continue to emerge at an ever-more rapid pace. Second, globalization brings with it new markets, new customers, nontraditional competitors, and new challenges. Third, the internet has created much greater transparency to any company's strategy, actions, and performance. As a result of these forces, companies find that their strategies need almost constant redefinition either because the old assumptions are no longer valid, because the previous strategy has been imitated and neutralized by competitors, or because technological developments and globalization offer unanticipated opportunities. Rooted in these premises, the leadership challenge is: How to successfully create the future (Boxes 2 and 3) even while managing excellence in the present (Box 1).

Take the case of the automotive industry. In the early 20th century, Ford innovated the mass-market for automobiles with the Model T. The core competence of the automotive industry for the past 100 years has been mechanical engineering — designing engines and pistons. There are major nonlinear shifts impacting automobile companies: driverless cars, electric cars (e.g., Tesla), and sharing economy (e.g., Uber). Ford must continue to improve the efficiency of its Box 1 business (gasoline-powered automobiles) even while building new competencies in computer science, artificial intelligence, and robotics (Box 2 and Box 3 imperatives).

GE is another case in point. In the past 15 years, under Jeff Immelt's leadership, GE has divested many businesses: insurance, NBC Universal, and more recently, finance. This is a Box 2 move. GE is transforming itself from industrial company to information company. GE's products such as aircraft engines, CT scanners, and turbine engines generate lots of data that is useful for its customers. GE has set up a Digital Business Unit to create and capture value from this information using Big Data analytics. GE can sell the information products to its customers such as airline companies, hospitals, and utilities in order to improve their efficiency. This is a Box 3 move.

Specific leadership challenges of The Three Box Solution are:

- How do we identify the market discontinuities (e.g., fundamental shifts in technology, customers, competitors, lifestyle/demographics, globalization, regulations, etc.) that could transform our industry?
- How do we analyze the opportunities and risks, as a result of our understanding of market discontinuities?
- How can we create new growth platforms (Box 3) with a view to exploit the market discontinuities?
- How do we selectively forget the past (Box 2)?
- What new core competencies must we build to support growth platforms?
- How do we allocate resources to support growth?
- What kind of organizational DNA must we have in order to anticipate and respond to changes on a continual basis?
- How do we execute breakthrough innovation strategies? L



3boxsolution.com

Taking Noninvasive Monitoring to New Sites and Applications™

For over 25 years, Masimo has been an innovator of noninvasive patient monitoring technologies, striving to improve patient outcomes and reduce the cost of care by taking noninvasive monitoring to new sites and applications.

Masimo offers leading technology to care providers across the continuum of care—including Emergency Medical Services (EMS), long-term care facilities, physician offices, and other post-acute care areas.[1]

www.masimo.com

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

[1] *Products shown may not be available for use in all care areas.*

Masimo

PLCO-000008/PLLT-10003A-0416

Brilliant discoveries. Delivered.

We are Patheon, and we bring to bear 40 years of experience and expertise, from development to manufacturing. We also bring global reach. An industry reputation for being right on time, the first time. Supply chain solutions designed to simplify complexity and speed up the process. And a passionate belief that together we can make the world a healthier place.

Patheon®

A HEALTHIER WORLD. DELIVERED.