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NOVEMBER 2018

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VOLUME 38, Number 11

PHARM EXEC'S 2019 PIPELINE REPORT NEW BETS, WIDER THREATS



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Steadying the Path of Good Science

OF THE SIX THERAPEUTIC AREAS we chose to focus on in this year's *Pharm Exec* Annual Pipeline Report (see page 12), two are facing a crisis. One is Alzheimer's disease and the other is antibiotics. For all the activity in the Alzheimer's pipeline, reflected by the breadth and number of trials, the current science is not proving successful. Many large companies, realistic to the lack of promising science, have exited Alzheimer's. In antibiotics, which has a small pipeline but has made inroads in science, companies are exiting for a different reason: the financial equation doesn't make sense. Both TA areas are potential blockbuster markets. Alzheimer's doesn't lack funding and antibiotics suffers from an innovation problem.

For all the expense of drug development, the perception is that antibiotics should cost \$1 a pill. Unfortunately, market dynamics being what they are, there is the fact that future antimicrobials that prove effective against antibiotic-resistance will be required to be used sparingly to reduce the resistance cycle. Dr. Kenneth I. Kaitin, professor and director of the Tufts Center for the Study of Drug Development at the Tufts University School of Medicine, and a *Pharm Exec* EAB member, notes the paradox on page 22: "Society is willing to spend a lot of money on cancer drugs that will add just a few months to a patient's lifetime, but antibiotics, which could actually save patients' lives, are expected to be relatively cheap," he says.

Dr. Evan Loh, president, chief operating officer, and chief medical officer of Paratek Pharmaceuticals, recently spoke at an industry event, discussing his company's long history in the antibiotic space and its recent successes. On Oct. 2, FDA approved Seysara for the treatment of inflammatory lesions of non-nodular moderate to-severe acne vulgaris in patients nine years of age and older, and Nuzyra for adults with community-acquired bacterial pneumonia and acute skin and skin structure infections. Loh joked that Paratek didn't plan for the drugs to be approved on the same day, and then elaborated on the need to take advantage of the legal pathways that allowed the company to pursue development in this public health space, as well as the value of taking advantage of early scientific meetings with FDA.

Those legal pathways include the 2012 passage of Generating Antibiotic Incentives Now, or GAIN. As part of FDA's Safety and Innovation Act, GAIN provides manufacturers an additional five-year exclusivity period for antibiotics that treat serious or life-threatening infections.

In addition to GAIN, another pathway is the limited-population antibacterial drug (LPAD) pathway authorized in the 21st Century Cures Act that allows FDA to review and approve new antibiotics specifically for use in patients with unmet

medical needs. The draft guidance is under public comment, with an anticipated April 1 finalization. And FDA Commissioner Gottlieb continues his press on the antibiotics market.

Loh, who is also vice chair of the Antimicrobials Working Group, made up of biotech companies focused on antimicrobial development, said, "I think where those meetings could go wrong is if you are not really listening to the FDA and what it is suggesting, and what it is not saying." He also advised that it is very important to pay attention to CMC and ensure you have the right CMO.

There is a conundrum in science. If discoveries rely on venture capital to fund, many of those on that side of the world have a "herd mentality" and they focus on fads and themes. For example, the current oncology market that focuses on the rare vs. what the public needs, such as antibiotics, which is not seen as appealing. And regulatory authority pathways are just as important on the road to innovation, as indicated in Paratek's approvals.

Jay Galeota, president and chief operating officer, G&W Laboratories, and also a member of our EAB, said, "Antibiotics is the only market that is constantly reinventing itself (as bugs morph and become new, different, and resistant). The perceived lack of attractiveness is a big issue, which FDA and others recognize, yet recent incentives do not seem to be enough to spark renewed interest in discovery and development here. Considering the most expensive hospital bed by far is the septic, isolated ICU one, something seems out of balance."

And it is out of balance. If the science of Alzheimer's improves, just imagine cured a la hep C, what that would mean for not just quality of life, but also for the healthcare system? But would health payers actually pay for the curative therapy? The innovation of being able to address the adaptable bacteria crisis would also score major wins for the overall healthcare system as noted in Galeota's statement. Drug discovery is risky and innovative and good science should be rewarded.



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By Joseph Constance

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Emerging Biopharma

Southeast Biotech: Rising Tall in the Valley

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By Peter Young

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■ Getting approval for medical treatments for serious conditions is of high importance—are the right drugs getting faster #FDA approval?

Sparta Systems, @SpartaSystems

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■ "Delivering messages that do not coincide with the physician needs will very quickly lead to physicians' loss of interest and along with the possibility of losing a mutually beneficial relationship and most likely loss of sales."

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Episode 19: The CEO Career Pivot

Michelle and Christen speak with Mei Mei Hu, CEO of United Neuroscience, about how being open to pivoting from your original plan can create a number of opportunities for an executive and their company. bit.ly/2JqWJGk

Episode 18: Getting 'Real' on Data

Pharm Exec editors sit down with one of this year's Emerging Pharma Leaders, Christopher Boone, the head of real-world data and analytics at Pfizer. bit.ly/2Q7JzAZ

Episode 17: Commercializing Research

Martin Low and Philip Low, CEO and co-founder, respectively, of On Target Laboratories, talk with *Pharm Exec* editors about the ups and downs of

commercializing research that has been previously shelved—and share their strategy in approaching a potential partner to license their technology. bit.ly/2ImLIW5

Episode 16: Rise of Specialty Pharma

Pharm Exec editors discuss the topic of specialty pharma—featured extensively in our September issue—touching on the areas of marketing, logistics, pricing, and other challenges executives in this once-niche market face. bit.ly/2MMORij

Episode 15: Robotics in Pharma

Learn how life sciences companies are using robotics and AI to enhance patient care, what the funding landscape is in this sector, and what C-suite members need to do now to be at the forefront of this emerging technology. bit.ly/2Pk8MqP



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High-Risk Marketing Violations Draw Scrutiny

Regulators, prosecutors shifting enforcement focus from off-label promotion to messages that raise safety issues, mislead

Much has been made of the decline in FDA warning and “untitled” letters citing pharma companies for violating marketing and communications requirements and policies. It may be that marketers are being more careful to avoid serious violations, observe some experts. But the change may be due more to the agency’s shift in enforcement focus to actions that raise serious safety issues, as opposed to overstepping disclosure rules. In recent comments, Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), noted that FDA’s Office of Prescription Drug Promotion (OPDP) is being very careful to issue enforcement letters that challenge actions that could lead to patient harm, as opposed to practices involving unlabeled uses.

This approach was emphasized by FDA regulators and legal experts at the Advertising and Promotion Conference sponsored by the Food and Drug Law Institute (FDLI) in October in Washington, D.C. They noted that enforcement efforts now focus on marketing messages that raise safety concerns, such as minimization of risk on opioid medications and other therapies with boxed warnings on labels—as opposed to communications that convey off-label information that may be truthful and non-misleading. OPDP Director Tom Abrams

cited a warning letter for sleep-aid therapy Zolpimist that omitted important risk information and labeled warnings on the product’s webpage. He also highlighted inadequate disclosures for opioid antagonist CONZIP, despite the product’s boxed warning describing extensive limitations of use. Recent OPDP letters similarly object to the failure to communicate serious risks related to an extended release oxycodone product and the minimization of serious risks for an epilepsy drug with a boxed warning describing important safety issues.

Similarly, the Center for Biologics Evaluation and Research (CBER) recently challenged the manufacturer of a recombinant Factor IX treatment for hemophilia B. The promotional material indicated that Idelvion may have much longer effectiveness than indicated and may encourage patients to engage in possibly dangerous activities.

Attorney John Bentifoglio reported that the Department of Justice also has shifted the focus of its pharma marketing enforcement program to violations involving products with boxed warnings or Risk Evaluation and Mitigation Strategies (REMS), where false and misleading communications may pose serious risks to patient health, and away from cases related to off-label promotion. Recent DOJ enforcement actions have involved failure to communicate

risks related to a diabetes medication and for a diagnostic that produced false test results. Peter Pitts, president of the Center for Medicine in the Public Interest, commented that FDA is shying away from challenging promotional activities that raise First Amendment issues and shifting enforcement actions to “egregious acts” that FDA needs to stop.

Science drives communications

This shift in emphasis also reflects scientific advances that has made FDA’s evaluation of the benefits and risks of innovative drugs more complex and more sophisticated, observed FDA Chief of Staff Lauren Silvis at the FDLI conference. Approved labeling is the central tool in devising advertising and promotion messages, Silvis pointed out, but continued scientific and medical advances highlight the need for FDA to be able to update initial labeling as new information emerges, particularly in a world of digital technologies, smartphones, and social media platforms. In response, FDA medical product centers are taking steps to better align product labeling and communication to incorporate additional clinical findings important to public health.

Recent advisories aim to advance the accuracy and relevance of prescription drug promotion, Silva added, as seen in a new guidance on presenting quantitative efficacy and risk information in DTC promotional labeling and advertisements. FDA describes strategies for sponsors to present such information on drugs and biologics that consumers can understand, including the use of charts and graphs to better illustrate quantitative data on drug benefits and side effects. **PE**



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Fighting for a Streamlined European HTA Scheme

Parliament throws wrench in Commission's plan to regulate HTA

Anyone wanting a bird's-eye view of the political operating context for the European pharmaceutical industry need look no further than this autumn's debates on health technology assessment (HTA)—and particularly the European Parliament's view of how to regulate it.

The parliament reached its opinion on this complex legislative proposal in early October. Compared to the European Commission's original plan for a streamlined European-level HTA, the parliament wants to put the brakes on. For the parliament, an EU-level assessment isn't enough. They want Europe's numerous national and regional HTA bodies to retain the right to run some of their own checks, even after the joint assessment in the Commission's proposal.

As far as drug companies are concerned, that won't work. The European industry backed the Commission's proposal when it came out in the spring, because it believed an EU-level HTA could speed and simplify a process that was becoming increasingly complicated in Europe's fragmented market. It would, industry hoped, eliminate the duplication and delay and discord arising from a multiplicity of local HTA bodies.

But if each local HTA body is going to continue running its own "complementary assessments"—as the parliament calls the opt-out it wants to create—then the in-

dustry sees a risk that it will face not just a persistent inconsistency among HTAs in each member state, but an additional—and valueless—HTA at the EU level, too. An extra barrier, rather than a reduction in barriers.

In addition, the parliament wants to exact a heavy price from drug firms for making use of the envisioned new system—not so much in money, but in terms of conditions and requirements for evidence, and in disclosure of information. The list of what the parliament wants to see as supportive evidence for an application for an HTA runs to several pages. Its belt-and-braces approach would generate delay, impose demands not always necessary, and discourage rather than bring speed and simplicity.

The parliament's lengthy requirements start with demanding that companies must present "all available up-to-date documentation containing the information, data, and studies, including both negative and positive results, that is necessary for the joint clinical assessment. That documentation shall include the available data from all tests performed and from all the studies in which the technology was used."

It also demands that the supportive data that industry provides should be made public, with only the scantest safeguards for commercial confidentiality. It repeatedly warns against conflicts of interest, and puts all the emphasis on transparency and data disclo-

sure: "Transparency and public awareness of the process is essential. All clinical data being evaluated should have, therefore, the highest level of transparency and public awareness in order to gain confidence in the system. In case there is confidential data for commercial reasons, the confidentiality needs to be clearly defined and justified and the confidential data well delimited and protected."

In response to these demands, the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), representing smaller firms, as well as the European Federation of Pharmaceutical Industries and Associations (EFPIA), said: "We regret that the European Parliament introduced the requirement that all clinical trial data should be submitted by health technology developers."

Shutting industry out?

To make matters worse, the opportunities for drug companies to be involved in the assessment process are heavily reduced in the parliament's take on the system. The parliament has eliminated or diluted several of the Commission's initial recommendations for constructive interaction. Some industry-friendly Members of the European Parliament (MEPs) attempted to reinstate them during the debates over the proposal, with a new provision that the assessors "shall meet with relevant health technology developers to define the scope of the assessment and the available up-to-date documentation to be submitted," but this was rejected in the parliament's final vote.

And as if all that wasn't enough, the parliament's opinion is laced with clauses that display skepticism, even hostility, to the drug industry, with criticism

implicit and explicit to pricing practices, to the value of its products, and to the principles behind its research.

It repeats the allegation—made by EU health ministers two years ago—that “the main barriers to access are the lack of new treatments and the high price of medicines, which in many cases do not have added therapeutic value.” It points a critical finger at what it sees as current deficiencies in drug evaluation: “Marketing authorizations are not accompanied by a comparative effectiveness study.” It turns its back on any suggestion that innovation should benefit those who generate it, championing “innovation which offers the best outcomes for patients and society as a whole,” and it focuses the legislation on a “high level of health protection,” rather than its original aim of speeding market access and boosting competitiveness.

The distrust of the private sector among MEPs is evident in its view that HTA should be promoted as a mechanism for “steering research strategically” and for “more efficient research.” And for the parliament, of equal importance to bringing innovations to patients is the deployment of HTA as a “help in decision-making on divestment in cases where a technology becomes obsolete.”

And these were just some of the milder comments expressed by MEPs during the evolution of the parliament’s opinion. Some wanted the assessment to go much further—even intruding into economic and social aspects. Far-left Czech MEP Katerina Konecna said in an early debate on the proposal: “I dislike the lack of an obligatory evaluation of the cost of a medicine. It is a mistake to exclude the social, ethical, and

economic aspects of evaluation.” Romanian socialist Maria Grapini wanted a direct link to achieving “the best cost-effectiveness ratio.”

Council’s hard line

If things are difficult in the parliament, it’s going to be seen as a walk in the park compared to the battles that are about to be waged in the other branch of the EU legislative machinery, the Council of Ministers. At least the

text must be changed.” The Bulgarian presidency, after testing the waters in the Council in the early summer, concluded that “member states have not identified mandatory uptake of joint HTA as a necessary solution.” Some countries questioned whether the duplication that the proposal aims to reduce is in itself a problem, and suggested that diversity among national assessments was an argument against rather in fa-

The parliament wants to exact a heavy price from drug firms for making use of the envisioned new system—not so much in money, but in terms of conditions and requirements for evidence, and in disclosure of information


parliament has paid lip service to the idea of removing duplication. But in the Council, some of the biggest member states are digging their heels in deeply at the Commission’s proposal.

At the top of this list of dislikes is what critical member states see as an unjustified and unwanted intrusion into their own autonomy for making decisions on anything to do with the pricing and reimbursement of drugs. And that is closely followed by their flat refusal to entertain any obligation to use an EU-level assessment instead of their own: for them, they know best how to judge what their patients need, and they don’t want other member states’ views to get in the way of that—much less a view from a consortium of member states.

Under the Commission proposal, “national decision-making capacity of member states is compromised,” France and Germany stated in a direct challenge. “The

vor of harmonization. And others argued that the Commission aim of limiting joint assessment to the clinical aspects alone is “practically impossible,” claiming that it is unrealistic to separate the clinical part of the assessment from the economic part.

Small wonder, then, that EFPIA Director General Nathalie Moll claims to be bewildered in her reaction to the situation. “The proposed HTA regulation is not, or at least should not be complicated,” she says. The joint HTA reports will be written by member states for member states, so “how can one object to the use of reports that one has been part of developing?” she asks. “It is difficult to see why member states would need to complement joint reports with additional national data.”

That is where the European drug industry will have to win its campaign in the coming months if it really wants a simplified and streamlined HTA system. 

2019 PIPELINE REPORT: New Bets, Tackling Wider Threats



As CAR-T therapy eyes new territory—solid tumors—and expands into autoimmune disease, other frontiers in drug development are beginning to open up. They highlight the raw promise of science, with cannabis-based agents targeting CNS and rare genetic disorders, as well as the larger responsibility to public health, including advancing non-opioid alternatives, addressing antibiotic resistance, and untangling the path to market in the still-contentious US biosimilars arena

By Joseph Constance

Where is science taking the future of medicine? *Pharm Exec's* 15th Annual Pipeline Report explores those possibilities ahead, with in-depth overviews of the most active, emerging—and critical—areas of therapeutic focus in biopharma R&D today. As in years past, promising product candidates in each category are highlighted—the new targets, new modalities, and new technologies paving the road from basic science to potential commercial success and ultimately an impact on the wider healthcare ecosystem.

Pharm Exec would like to acknowledge Pharma Intelligence, part of Informa Group plc, for providing supportive data in the report and accompanying charts.

Advancing CAR-T

From leukemia to lymphoma, advances in diagnosing and treating blood cancers have optimized survival rates. Efforts involving chimeric antigen receptor (CAR)-T (gene) therapy are transitioning from blood cancers to a new target: solid tumors. Recent efforts involve both CAR-T therapies and tumor agnostic drugs—treatments specifically directed at cancers that contain certain molecular signatures.

Kindling hope for patients was the FDA approval in 2017 of Novartis' Kymriah for treating acute lymphoblastic leukemia (ALL) in certain pediatric and young patients, and Gilead Sciences/Kite Pharma's Yescarta, for adults with certain large B-cell lymphomas. Also making a move in the CAR-T arena was Celgene, which acquired Juno Therapeutics in January 2018. Juno has pioneered CAR-T and TCR (T-cell receptor) research, establishing a portfolio with potential therapies for several cancer indications. Added to Celgene's lymphoma program is JCAR017, a CD19-directed CAR-T product in a pivotal program for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). FDA approval may come in 2019. The drug has potential global peak sales of about \$3 billion.

While the scientific road for CAR-T does not dead-end with hematologic cancers, therapies for solid tumors are challenging because the tumors are surrounded by a hostile, immuno-suppressive environment that keeps CAR-T cells out. They must be engineered with components that increase their activity in these environments.

"Lots of eyes will be watching the feasibility of CAR-T therapies on the market as uptake has been slow," says Madelyn Hanson, manager, oncology consulting services, clinical and scientific assessment, at Kantar Health. "Many do hope that CAR-Ts can hit the mainstream, and that more cell therapies are able to achieve what has been seen already with approved therapies."

In August, Seattle Children's Hospital initiated a CAR-T cell trial for children and young adults who have relapsed or refractory non-central nervous system epidermal growth

factor receptor (EGFR)-expressing solid tumors. In the Phase I trial, STRIVE-01, CAR-T cells target the EGFR protein expressed in childhood sarcoma, kidney, and neuroblastoma tumors. Scientists will engineer CAR-T cells with the EGFR806 antibody that has significant antitumor activity. It may selectively recognize tumor cells expressing EGFR.

Other solid tumor efforts

Besides CAR-T, other adoptive cell transfer (ACT) therapies are targeting solid tumors. Also in research are TCR-engineered T cells. Locating proteins on tumor cells that are not present in normal tissue has been an impediment, notably regarding solid tumors.

Present in T cells, TCRs are natural receptors that recognize peptides derived from chopped proteins that may include antigens specific to cancer cells. TCRs recognize proteins that are not present in the plasma membrane—a requirement for CARs. This broadens the potential for targeting more proteins found on tumor cells.

RXi Pharmaceuticals is developing immuno-oncology therapeutics, to be used with ACT, based on its self-delivering RNAi (sd-rxRNA) platform. The process uses immune cells, such as T-lymphocytes, that are isolated from the patient or retrieved from allogeneic immune cell banks, and then expanded to express tumor-binding receptors.

Also addressing solid tumors are Tarveda Therapeutics' Pentarins—powerful and selective miniature drug conjugates with high affinity for specific cell surface and intracellular targets. Pentarins bind to tumor cell targets and offer sustained release into solid tumor tissue.

CAR-T DRUGS IN CLINIC	
PROTEIN TARGET	# of agents
CD19 MOLECULE	64
TNF RECEPTOR SUPERFAMILY MEMBER 17	19
CD22 MOLECULE	11
MEMBRANE-SPANNING 4-DOMAINS, SUBFAMILY A, MEMBER 1	10
PROGRAMMED CELL DEATH 1	9
EPIDERMAL GROWTH FACTOR RECEPTOR	7
ERB-B2 RECEPTOR TYROSINE KINASE 2	7
MESOTHELIN	6
MUCIN 1, CELL SURFACE ASSOCIATED	6
WILMS TUMOR 1	5
INTERLEUKIN 3 RECEPTOR, ALPHA (LOW AFFINITY)	5
CD33 MOLECULE	4
FOLATE HYDROLASE (PROSTATE-SPECIFIC MEMBRANE ANTIGEN) 1	4
RECEPTOR TYROSINE KINASE-LIKE ORPHAN RECEPTOR 1	4
CD28 MOLECULE	3
CANCER/TESTIS ANTIGEN 1	3
GLYPICAN 3	3

Source: Pharmaprojects® | Pharma Intelligence, Sept 2018

FAST FOCUS

» Oncology remains the most active therapeutic area when it comes to industry partnership deals. According to Pharma Intelligence's Medtrack, from the second half of 2017 through the first half of 2018, oncology represented 24% of total deal volume. The next-highest specific therapeutic category was CNS, at 14%, followed by diagnostics, at 9%.

» While growth in the pipeline has picked up in many indications, statistics continue to illustrate the risky nature of clinical development. Pharma Intelligence found that 3,807 drugs entered the pipeline during 2017 as 3,412 left development, a net increase of just 395 and a churn rate of over 20%.

» According to EvaluatePharma, orphan drug products currently in R&D will account for 35%-38% of sales generated from pipeline products from 2018 to 2024. And of the top 20 orphan drugs in the pipeline today, 40% could be blockbusters.

STEERING CAR-T DEVELOPMENT	
SPONSOR	# of trials
(OTHER HOSPITAL/ACADEMIC/MEDICAL CENTER)	362
NATIONAL INSTITUTES OF HEALTH/NATIONAL CANCER INSTITUTE	84
UNIVERSITY OF PENNSYLVANIA	37
(OTHER INDUSTRY SPONSOR)	30
CELGENE/JUNO THERAPEUTICS	28
BAYLOR COLLEGE OF MEDICINE	20
TAKARA BIO	20
INNOVATIVE CELLULAR THERAPEUTICS CO.	19
NOVARTIS	19
BELLICUM PHARMACEUTICALS	18
GILEAD SCIENCES/KITE PHARMA	18
MD ANDERSON CANCER CENTER, UNIVERSITY OF TEXAS	18
FRED HUTCHINSON CANCER RESEARCH CENTER	15
TEXAS CHILDRENS HOSPITAL	15
(OTHER GOVERNMENT AGENCY)	14
ADAPTIMMUNE	14
CITY OF HOPE COMPREHENSIVE CANCER CENTER	13
(OTHER COOPERATIVE GROUP)	12
MEMORIAL SLOAN-KETTERING CANCER CENTER	12
CARsgen THERAPEUTICS	11

Source: Pharmaprojects® | Pharma Intelligence, Sept 2018

Tarveda's lead Pentarin clinical drug candidate, PEN-221, targets the somatostatin receptor 2 (SSTR2) to treat patients with tumors, including neuroendocrine, small cell lung, and other cancers, which express SSTR2. PEN-221 has a peptide highly selective for SSTR2. It is in a Phase IIa trial in patients with gastrointestinal midgut neuroendocrine tumors, pancreatic neuroendocrine tumors, or small cell lung cancer.

“Lots of eyes will be watching the feasibility of CAR-T therapies on the market as uptake has been slow.”

Meanwhile, Erytech's pivotal Phase III trial with eryaspase in second-line pancreatic cancer is open for enrollment. The company is launching a Phase II trial in first-line triple-negative breast cancer.

Tumor agnostic therapies

Novel therapies that target genetic mutations independent of where a tumor is located—tumor agnostic therapies—represent a new paradigm in solid tumor treatment. Unlike drugs that target specific biomarker-positive tumors, tumor agnostic therapy is based on a biomarker that determines the disease regardless of its location in the body. Such an approach might make it easier to match patients to the best clinical trial and the best treatment.

In May 2017, Merck & Co.'s checkpoint inhibitor immunotherapy, Keytruda, became the first FDA-approved cancer treatment that was based on whether a tumor had a specific genetic mutation, not specifically on the organ in which the tumor arose. In September, the European Commission approved Keytruda, in combination with pemetrexed (Alimta), and platinum chemotherapy, for first-line treatment of metastatic nonsquamous non-small cell lung cancer (NSCLC) in adults whose tumors have no EGFR- or anaplastic lymphoma kinase (ALK)-positive mutations. But in April,

a Phase III trial assessing the combination of Incyte's lead cancer immunotherapy candidate, epacadostat, and Merck's Keytruda in melanoma was halted after the combo therapy failed the pivotal study.

Recently though, IMV, a clinical-stage immuno-oncology company, expanded its clinical program by collaborating with Merck to undertake a significant basket trial. In the Phase II study, scientists will evaluate IMV's lead candidate, DPX-Survivac, in combination with low-dose cyclophosphamide and Keytruda, in patients with certain advanced or recurrent solid tumors, such as bladder, liver, and ovarian tumors, among others.

Historically, clinical trials, even for a single biomarker, are done in a specific tumor type. This is not the case with tumor agnostic therapies. Hanson expects these drugs to reach more patients much faster because tumor agnostic therapies will not be undergoing multiple clinical trials for individual tumor types. Unfortunately, she explains, some physicians are unsure as to which tumors they can treat with these therapies.

Using the tumor agnostic approach, Loxo Oncology is developing its tropomyosin receptor kinase (TRK) fusion inhibitor, larotrectinib. TRKs are abnormal proteins that promote tumor cell growth. The compound stops TRK fusion activity. Larotrectinib is in a Phase II basket trial for solid cancers harboring TRK alterations, such as tumors of the central nervous system. Another TRK inhibitor, Loxo-195, for potential acquired resistance in patients receiving larotrectinib or multikinase inhibitors with anti-TRK activity, is in a currently enrolling Phase I/II trial.

Meanwhile, Roche plans to file for approval of entrectinib, which the company acquired when it bought Ignyta in 2017. In September, Roche reported that entrectinib shrunk tumors in 77.4% of those with locally advanced or metastatic ROS1-positive NSCLC. Entrectinib also shrunk tumors in more than half of people with cancer in the central nervous system.

CAR-T's next frontier: Autoimmune disease

CAR-T therapies are also being explored in the fight against autoimmune diseases. Most current treatments only control symptoms, but scientists in early research at the University of

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OPIOID REACH	
DISEASE FOCUS IN CLINIC	# of drugs
PAIN, NOCICEPTIVE, GENERAL	121
PAIN, CANCER	37
PAIN, POST-OPERATIVE	36
PAIN, MUSCULOSKELETAL, ARTHRITIS	29
PAIN, MUSCULOSKELETAL, UNSPECIFIED	23
PAIN, NEUROPATHIC, GENERAL	18
ADDICTION, NARCOTIC/OPIATE	8
NEUROPATHY, DIABETIC	5
MIGRAINE	4
PAIN, POST-HERPETIC	4
ANAESTHESIA, ADJUNCT	3
ANXIETY, UNSPECIFIED	2
DEPRESSION, MAJOR DEPRESSIVE DISORDER	2
PRURITUS	2
ADDICTION, DRUG, UNSPECIFIED	1
ANAESTHESIA	1
ARTHRITIS, OSTEO	1
ATTENTION DEFICIT HYPERACTIVITY DISORDER	1
CONSTIPATION, OPIOID-INDUCED	1
DEPRESSION, UNSPECIFIED	1

Source: PharmaProjects® | Pharma Intelligence, Sept 2018

Pennsylvania have used CAR-T technology as a key component of a strategy to remove the subset of antibody-making cells that cause autoimmune disease, without harming the rest of the immune system.

In October, Sangamo Therapeutics acquired TxCell, which is developing personalized T cell immunotherapies for treating severe inflammatory and autoimmune diseases with high unmet medical need. The company is harnessing regulatory T cells (CAR-Treg). Sangamo is targeting transplantation and other autoimmune diseases, both T-cell and B-cell mediated, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases, and inflammatory skin diseases. The company's TX200 for transplant rejection is in the preclinical stages, with a clinical trial application filing planned for the first half of 2019.

Atara Biotherapeutics has also expanded its collaboration with Memorial Sloan Kettering Cancer Center to develop the next generation of CAR-T immunotherapies, targeting oncology, autoimmune, and infectious diseases.

Confronting the opioid crisis

On a backdrop of public outcry and increased litigation against opioid makers, non-opioid therapies are in demand. And the potential market size is a driver. BCC Research estimates the global non-opioid pain treatment market to reach about \$22 billion in 2022. FDA is encouraging development of alternatives and aims to publish documentation facilitating

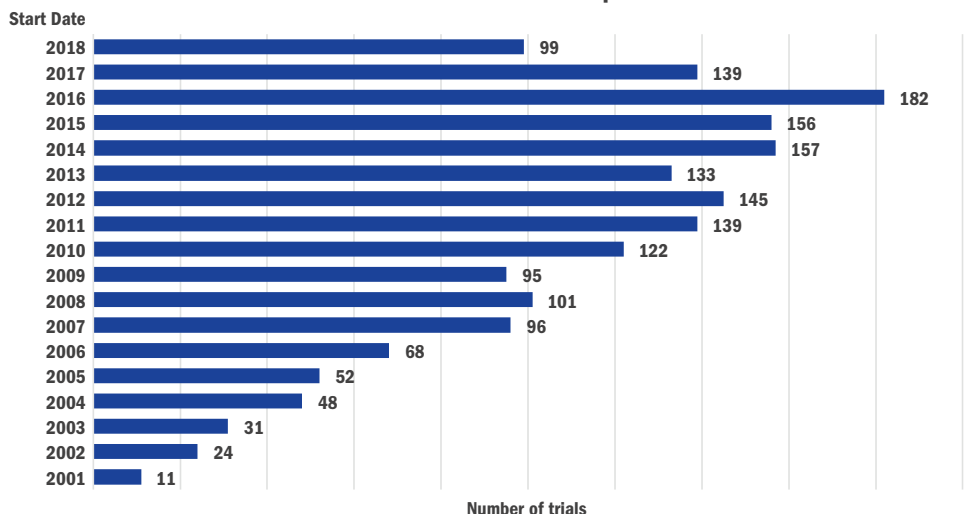
drug development targeting specific pain types. The idea behind this approach is smaller clinical trials and more rapid drug approvals.

In terms of drug development activity, Nektar Therapeutics' NKTR-181, in Phase III, is a form of oxycodone to which is linked polyethylene glycol. For treating moderate-to-severe chronic low back pain, the candidate causes a slower release of dopamine. Meanwhile, Astraea Therapeutics' AT-121 is in preclinical development, in investigational new drug (IND)-enabling studies. The therapy stimulates two molecules in the brain simultaneously: MOR, the μ -opioid receptor, and the nociceptin opioid receptor (NOR). When activated in the brain, NOR reportedly acts against MOR. But, simultaneously, NOR reinforces MOR's pain-relieving activity in the body's central nervous system.

In September, Aptinyx highlighted preclinical data on its novel N-methyl D-aspartate (NMDA) receptor modulator, NYX-2925, that support the company's ongoing clinical development for treating chronic pain. The drug is in Phase II trials for painful diabetic peripheral neuropathy and fibromyalgia. The data demonstrate strong mechanistic support for developing NYX-2925 as a potential therapy for chronic pain conditions. FDA has granted fast-track designation to NYX-2925 for treating neuropathic pain associated with diabetic peripheral neuropathy.

Recro Pharma is developing non-opioid products for acute pain. The company's lead

Clinical trials initiated in opioids



Phase I-IV clinical trial starts of opioid drugs, 2001 to 2018. Note: Trial numbers are limited to those for which a start date is provided in the public domain. The numbers for recent years may also be impacted by delayed reporting of trial activity.

Source: TrialTrove® | Pharma Intelligence, Sept 2018

candidate is a proprietary injectable form of meloxicam. This intravenous (IV) meloxicam has successfully completed several Phase II clinical trials for treating moderate-to-severe pain. Recro has responded to an FDA complete response letter regarding its new drug application (NDA) for NYX-2925, resubmitting the NDA with revised language relating to the product label and more data involving extractable and leachable items.

Tremeau Pharmaceuticals is developing TRM-201 (rofecoxib) as a fast-track, first-approved treatment for hemophilic arthropathy, for which high-potency opioids are currently used. The company also is developing TRM-359 (etoricoxib) as a breakthrough, first-approved therapy for a serious pediatric orphan disease treated now using high-potency opioid drugs.

In September, Purdue Pharma announced that it is providing \$3.4 million to Harm Reduction Therapeutics to develop its OTC naloxone nasal spray. The opioid antagonist naloxone counteracts the effects of a life-threatening opioid overdose.

New world of cannabis

A lack of standardized tests for the cannabis plant impedes scientific-based evaluations of test results usually required of approved therapeutics. Standardized testing would clarify concerns about potency, actual cannabidiol (CBD) content, and the presence of residual contaminants.

These issues will almost certainly be worked out, however, and have not stopped a slew of companies from moving forward in developing prescription therapies, targeting several disorders, including autism, schizophrenia, cystic fibrosis, and fibromyalgia, among others.

This past summer marked a milestone when FDA approved the first prescription pharmaceutical derived from the cannabis plant, GW Pharmaceuticals' lead cannabinoid compound, Epidiolex, an oral solution for treating seizures associated with Dravet and Lennox-Gastaut syndromes in patients two-years old and older. Both diseases are rare, severe forms of childhood-onset epilepsy that are treatment challenges.

In late September, the Drug Enforcement

Administration (DEA) approved CBD as a Schedule V controlled substance. The order places FDA-approved drugs that contain CBD derived from cannabis and no more than 0.1% tetrahydrocannabinols (THCs) in Schedule V, allowing for its sale in the US by GW Pharmaceuticals and opening the door for other companies to sell cannabis-based therapeutics.

There are still issues to be addressed, however, such as the unfamiliarity with cannabis on the part of some physicians, who may hesitate to write prescriptions. GW's plan to educate physicians on the benefits of Epidiolex has involved hiring more than 60 neurology sales reps who will target about 5,000 epilepsy specialists.

Standardized testing would clarify concerns about potency, actual cannabidiol content, and the presence of residual contaminants

Epidiolex is also in Phase III clinical studies for treating tuberous sclerosis. GW's Sativex is an oromucosal spray of a formulated extract of the cannabis sativa plant that contains cannabinoids delta-9-THC and CBD in a 1-to-1 ratio, as well as other cannabinoids and non-cannabinoids.

In Europe, Sativex has marketing authorization in 21 countries for treating spasticity, muscle stiffness, and spasm caused by multiple sclerosis. In the US, the drug is in Phase III testing for MS spasticity. Cannabidivarin (CBDV) is a non-psychoactive cannabinoid that does not cause euphoria. GW is developing it for epilepsy and autism spectrum disorders.

Elsewhere, Nemos Bioscience has seven drugs in early-phase development. Among them are NB1111, a prodrug THC for treating glaucoma, and NB1222, also a prodrug THC, for treating chemotherapy-induced nausea and vomiting. Both candidates are in the pre-clinical stage.

Zynerba Pharmaceuticals' pharmaceutically-produced CBD and lead-product candidate, ZYN002, is under evaluation in several rare

CANNABINOIDS IN CLINIC	
PHASE	# of trials
II	232
I	143
III	90
IV	81
I/II	38
II/III	21

Source: Trialtrove® | Pharma Intelligence, Sept 2018



Expert analysis
of medical
marijuana changes
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CANNABINOIDS INVESTMENT

SPONSOR TYPE	# of trials
ACADEMIC	311
INDUSTRY, ALL OTHER PHARMA	259
CT.GOV	65
GOVERNMENT	58
INDUSTRY, TOP 20 PHARMA	38
COOPERATIVE GROUP	20
NOT-FOR-PROFIT FUNDING ENTITY	9
MISCELLANEOUS	5
INDUSTRY, GENERIC	2
NATURAL PRODUCTS, OTC, COSMETICS	2

Source: Trialtrove® | Pharma Intelligence, Sept 2018

and near-rare neuropsychiatric disorders. It is a gel that is in pivotal studies for fragile X syndrome. ZYN002 has completed Phase II studies for developmental and epileptic encephalopathies and Phase II trials for adult refractory focal seizures.

Corbus Pharmaceuticals is developing lenabasum, a synthetic, oral, small-molecule, selective cannabinoid receptor type 2 (CB2) agonist that showed in animal studies to preferentially bind to CB2 expressed on activated immune cells and fibroblasts. Activation triggers physiologic pathways that correct inflammation, speed bacterial clearance, and halt fibrosis. The candidate is in Phase III clinical studies for systemic sclerosis and dermatomyositis; and in Phase II trials for systemic lupus and cystic fibrosis.

In September, Corbus licensed from Jenrin Discovery the exclusive worldwide rights to candidates from more than 600 compounds targeting the endocannabinoid system. The portfolio includes CRB-4001, a CB1 inverse agonist that is to enter a Phase I study in 2019 followed by a NIH-supported Phase II study.

Cara Therapeutics has evaluated CR701 in a rodent model of neuropathic pain that produces both hyperalgesia (sensitization of nerve endings to painful stimuli) and allodynia (painful perception of innocuous stimuli) comparable to human conditions. CR701 in animals with neuropathy significantly reversed hyperalgesia and allodynia.

Insys is developing a CBD oral solution for childhood absence epilepsy, infantile spasms, and Prader-Willi syndrome, a genetic disorder caused by a loss of function of certain genes. Kalytera is developing a clinical-stage CBD to prevent and treat graft-versus-host disease. The company also is designing a treatment for acute and chronic pain using a compound that consists of a cannabinoid conjugated with naproxen, a generic, non-steroidal, anti-inflammatory drug approved for treating pain. The goal is to develop a well-tolerated potent, non-psychotropic, oral analgesic for intractable pain.

Also in play is Artelo Biosciences, which is developing high-potency cannabinoid receptor 1 and 2 agonists. The candidates have completed Phase I trials for anorexia and cachexia, and are in preclinical work for cancer. In Au-

gust, Revive submitted an application to FDA seeking orphan-drug designation of CBD for treating hepatic ischemia and reperfusion injury during liver transplantation. Two months earlier, FDA had granted Revive orphan-drug status for CBD for treating autoimmune hepatitis.

In September, GB Sciences selected Catalent Pharma Solutions to provide oral delivery systems, formulation development, and clinical-scale oral dose manufacturing of GB Sciences' proprietary cannabinoid-containing active pharmaceutical ingredients for its Parkinson's disease therapies.

Biosimilar stagnation

FDA's approval of a dozen biosimilars so far trails noticeably behind activity in Europe, where the European Medicines Agency (EMA) has approved more than 40 biosimilars. In the US, many companies with brand products are pushing to delay competition. Makers of biosimilars have protested actions that block access to reference products needed for new drug testing. Pfizer filed a citizen petition with FDA asking the agency to halt misinformation on biosimilar safety and use from reference product manufacturers, citing false and misleading statements from innovators suggesting biosimilars are not as safe or effective as brands and have slowed prescribing and uptake of the new competitors.

More complex testing requirements push biosimilar development costs up to \$250 million per program, compared with \$10 million needed to produce a new generic drug

In its Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, the Department of Health and Human Services (HHS) stated that FDA would issue new policies to improve the availability, competitiveness, and adoption

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of biosimilars as affordable alternatives to branded biologics. Over the summer, FDA unveiled its Biosimilars Action Plan, listing initiatives for establishing a more efficient review process, including greater scientific and regulatory clarity for sponsors, and tools for using modern analytical techniques.

Still, there remain several regulatory issues to be considered, including testing requirements to document interchangeability; product naming to distinguish biosimilars from reference drugs and limit prescribing; and suggestions that switching from one interchangeable therapy to another raises additional safety concerns. Other key issues involve ongoing patent challenges and challenging payment policies that stymie biosimilar coverage

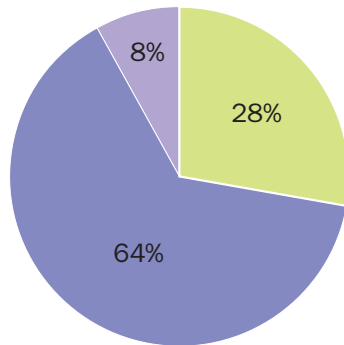
and prescribing. More complex testing requirements push biosimilar development costs up to \$250 million per program, compared with \$10 million needed to produce a new generic drug.

Despite the issues, research continues. In May, Coherus BioSciences resubmitted its biologics license application (BLA) for CHS-1701, a pegfilgrastim (Amgen's Neulasta) biosimilar candidate, to FDA using the 351(k) pathway. The company's CHS-1420 adalimumab (AbbVie's Humira) has completed Phase III clinical studies in psoriasis.

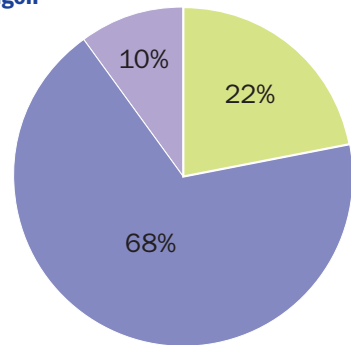
Novartis' Sandoz unit plans to launch several biosimilars of key oncology and immunology biologics by 2020, including an approved Erelzi, a biosimilar to Amgen's Enbrel, as well as biosimilars of Humira (adalimumab), Neulasta (peg-

BIOSIMILAR PENETRATION: IMPACT ON BIG PHARMA

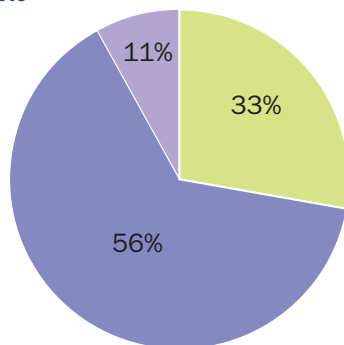
J&J



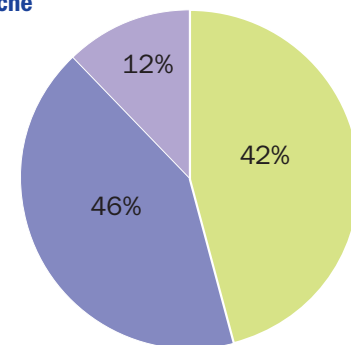
Amgen



AbbVie



Roche



■ Pipeline with biosimilars on the market
 ■ Pipeline not at risk of biosimilar erosion
 ■ Pipeline at risk in the next 5 years (biosimilars in development)

Based on reviews of the biologics pipelines and markets of key big pharma companies Johnson & Johnson, AbbVie, Amgen, and Roche, each company is compared by percentage of biologics not at risk of biosimilar erosion (no rival biosimilars in development or market), what percentage currently have competing biosimilars on the market, and what percentage are at risk of erosion in the next five years (rival biosimilars at a preclinical status through to pre-registration). Note: vaccine biosimilars in development were not factored in.

Source: Pharmaprojects® | Pharma Intelligence, Sept 2018

VACCINE BIOSIMILARS SNAPSHOT				
Product name	Active ingredient	Condition treated	Highest phase of development	Company name
DITANRIX	diphtheria toxoid, tetanus toxoid	diphtheria, tetanus	Marketed	GlaxoSmithKline plc, GlaxoSmithKline SpA, GlaxoSmithKline Espana
EG-HPV	human papillomavirus type 16 L1 capsid protein (recombinant), human papillomavirus type 18 L1 capsid protein (recombinant)	cervical cancer	Phase I	EyeGene Inc, Chong Kun Dang Pharmaceutical Corp
EPOTRUST	erythropoietin alfa (recombinant, human)	anemia associated with chronic renal failure	Marketed	Panacea Biotec Ltd
HEAT-STABLE ROTAVIRUS VACCINE	rotavirus (live)	rotaviral enteritis	Phase II	Merck & Co Inc, PAREXEL International Corp, MSD Wellcome Trust Hilleman Laboratories Pvt Ltd
INFLUENZA HA VACCINE	influenza virus hemagglutinin	influenza	Marketed	Daiichi Sankyo Company Limited, The Kitasako Institute
INTERMAX-ALPHA	interferon alfa-2a (recombinant, human)	hepatitis B, cancers	Marketed	LG Life Sciences Ltd, BioPartners GmbH

Source: Medtrack | Pharma Intelligence, Sept 2018

filgrastim), Remicade (infliximab), and Rituxan (rituximab).

Celltrion's pipeline contains six antibody biosimilars, including Remsima SC, (Janssen's Remicade) and CT-P16 (Genentech's Avastin). In August, Celltrion finalized trials for Remsima SC and intends to file a marketing authorization application to EMA late 2018. Its bevacizumab biosimilar, CT-P16, is ready for Phase III trials.

Amgen is involved on both sides of biosimilars. The company gained FDA approval for the first biosimilar version of AbbVie's Humira, as well as for its and Allergan's Mvasi, a biosimilar of Roche's blockbuster drug Avastin. But Amgen is fiercely defending its biologics portfolio, including Enbrel, Neulasta, and Neupogen from biosimilars made by others. Amgen also is in court against Sandoz over the patent validity and protection of Enbrel.

The pipeline is small for biosimilar vaccines. EyeGene and Chong Kun Dang Pharmaceutical are in Phase I trials with EG-HPV, a recombinant bivalent vaccine containing human papilloma virus HPV-16 and HPV-18 virus-like particles. It is for preventing cervical cancer caused by the human papillomavirus, according to Medtrack data.

Merck, the CRO Parexel, and Hilleman Laboratories—a partnership between Merck and Wellcome Trust—are in Phase II trials with a heat-stable rotavirus vaccine that elicits antibody responses that neutralize diseased antigens. The vaccine is indicated for preventing gastroenteritis caused by rotavirus infection, Medtrack reports.

Alzheimer's failing to fulfill

Les Funtleyder, healthcare portfolio manager at E Squared Capital Management, and a *Pharm Exec* Editorial Advisory Board (EAB) member, points out that “Nothing has worked for Alzheimer's, and nothing seems to be on the horizon.” He adds: “Investors would want a lot of certainty regarding a mechanism of action before they encourage pharma to put real money behind it.” And without functional outcomes with biomarkers, Funtleyder questions whether they would receive regulatory approval.

“We need to find a way to attack Alzheimer's disease and other forms of cognitive impairment early on,” says Dr. Edward I. Ginns, medical director, neurology for Quest Diagnostics. (Quest developed CogniSense, a cognition test available as an iPad app and given in the primary care doctor's office.) If researchers can go back and identify specific processes involved in cognitive impairment, they may find that some Alzheimer's interventions—which were not therapeutic when the brains neurons were beyond saving—might be successful at an earlier stage, Ginns adds. Another option, he says, might involve regenerative therapy that replaces neurons no longer active.

The frustration in the Alzheimer's space caused Pfizer to terminate its research efforts in Alzheimer's and Parkinson's diseases. And Eli Lilly's solanezumab did not have much positive effect in those with the mildest form of Alzheimer's disease. But in January, Johnson & Johnson and



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ALZHEIMER'S TESTING: GLOBAL REACH			
COUNTRY	# of drugs	COUNTRY	# of drugs
US	240	ITALY	43
UK	64	NETHERLANDS	37
CANADA	61	BELGIUM	35
SOUTH KOREA	56	SWITZERLAND	35
GERMANY	55	AUSTRIA	33
FRANCE	51	FINLAND	29
JAPAN	50	CHINA	27
SPAIN	50	IRELAND	25
SWEDEN	49	PORTUGAL	25
AUSTRALIA	43	DENMARK	24

Source: Pharmaprojects® | Pharma Intelligence, Sept 2018

Janssen Pharmaceuticals began working with the University of Pennsylvania's Gene Therapy Program, using adeno-associated virus (AAV)-vectors developed by the university and antibodies targeting Alzheimer's disease developed by Janssen. The effort harnesses AAV viral gene delivery to express therapeutic antibodies that target the main pathological hallmarks of Alzheimer's disease (see the most active clinical targets and mechanisms of action in Alzheimer's on page 24).

Earlier this year, Biogen and Eisai's Phase II results for BAN2401 generated some hopes for amyloid efforts. The compound is the humanized IgG1 version of the mouse monoclonal antibody mAb158, and targets beta-amyloid protein fragments that accumulate in the brain. While data showed that BAN2401 had a significant effect on cognitive decline in mild Alzheimer's patients at 18 months, newer results unveiled last month found that the drug may only work in a small subset of patients—those who carry the APOE4 protein. And these patients are reportedly also susceptible to brain swelling.

In other anti-amyloid activity, Genentech-Roche's antibody crenezumab was found in two Phase II trials to lower amyloid beta oligomer levels in the cerebrospinal fluid of most patients.

Need for novel antibiotics

Antibiotics, magic bullets that save thousands of lives, have become less effective thanks to resistant bacteria. Simple surgeries and other procedures might become extremely risky without antibiotics that can reliably prevent infection. In the US, at least two million people have an antibiotic-resistant infection, and at least 23,000 people die annually, according to the Centers for Disease Control and Prevention (CDC). The World Health

Organization (WHO) is warning that the current antibiotic pipeline will not be enough to combat future threats.

Dr. Kenneth I. Kaitin, professor and director of the Tufts Center for the Study of Drug Development at the Tufts University School of Medicine, and also a *Pharm Exec* EAB member, notes a paradox. "Society is willing to spend a lot of money on cancer drugs that will add just a few months to a patient's lifetime, but antibiotics, which could actually save patients' lives, are expected to be relatively cheap," he says. "As a result, companies hesitate to invest in developing new antibiotics."

Kaitin explains that there is "a less appealing reimbursement landscape" for drugmakers in the antibiotic space, compared with oncology therapeutics. Many companies have stopped investing in antibiotics development because of an inability to generate desired revenue, he adds. "Moreover, new scientific knowledge often drives innovative research activity," says Kaitin. "What is needed is more basic research to stimulate interest in developing novel antibiotics."

"New scientific knowledge often drives innovative research activity. More basic research is needed to stimulate interest in developing novel antibiotics."

Meanwhile, FDA is collaborating with other federal agencies and biomedical researchers to advance the science, regulatory policies, and reimbursement strategies to support innovation. The issue: payment and coverage policies for new drugs encourage widespread use of the products to generate a sufficient return on investment to companies sponsoring research on new treatments. But to remain effective against lethal pathogens, new antimicrobials must be used very sparingly, cutting revenues in the process.

FDA Commissioner Scott Gottlieb has outlined proposals for devising innovative milestone payments and subscription fees for developers of

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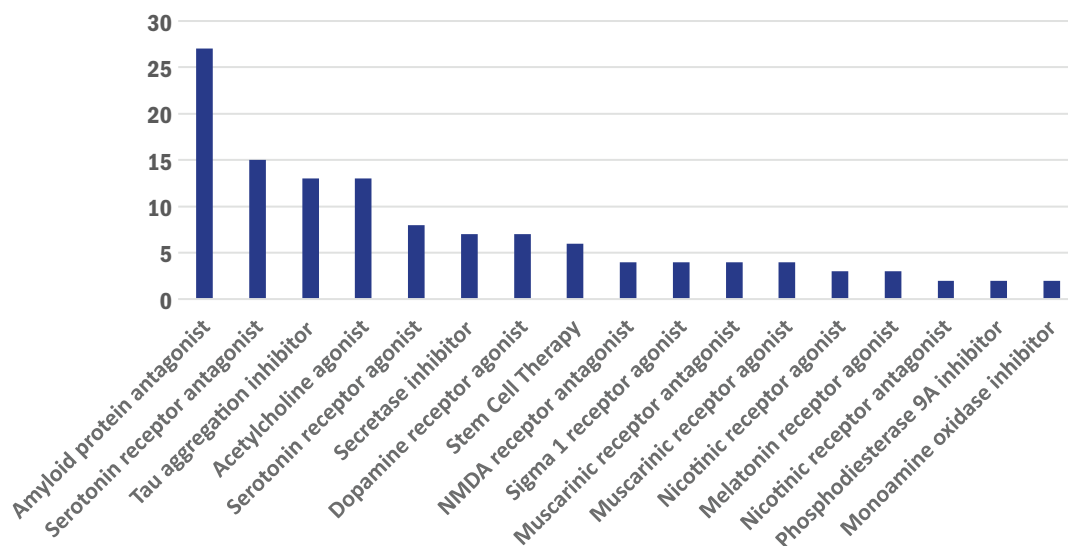
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Alzheimer's: Top Targets



The top 17 mechanisms of action of Alzheimer's disease drugs currently in the clinic.

Source: Pharma Intelligence, 2018

products targeted at multi-drug resistant organisms. But it remains to be seen if incentives will spark renewed interest in antibiotic discovery and development.

Drugs in late-stage development that WHO thinks are innovative and are expected to act against "priority" pathogens include Merck's relebactam in combination with imipenem/cilastatin (Phase III); Motif Bio's iclaprim, a targeted gram-positive antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (Phase III); Tetrphase's eravacycline (Xerava), approved in August by FDA for treating complicated intra-abdominal infections; and Paratek's omadacycline (Nuzyra), cleared by FDA in October for treating adults who have community-acquired bacterial pneumonia and acute skin and skin structure infection.

Also with high potential for fighting microbes of concern

are Shionogi's cefiderocol (S-649266), in Phase III studies targeting complicated urinary tract infections and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; and Polypor's murepavadin (POL7080), a novel highly specific outer membrane protein-targeting antibiotic in

Phase III trials for treating hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia caused by *Pseudomonas aeruginosa*.

Goals within reach

Despite encountering failures along the way, society depends on science to solve the issues and challenges caused by disease. This is readily seen with CAR-T, a living therapy that is offering hope for many.

Science has the chance to pull us across the goal line in the fight against the opioid epidemic, while at the same time generating new opportunities and treatments in the cannabis arena. The challenges are tougher in Alzheimer's disease and in antibiotic resistance, where novel therapeutics are needed in both, but for the latter, may finally be reaching patients. Essentially, as today's biopharma pipeline illustrates, it's a matter of continued perseverance. **PE**



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SCIENCE AND SYNERGY

THERAPY AREA	# of deals
ONCOLOGY	772
OTHER*	623
CENTRAL NERVOUS SYSTEM	339
DIAGNOSTICS	277
INFECTIOUS DISEASES	240
ENDOCRINE, METABOLIC, AND GENETIC DISORDERS	168
IMMUNOLOGY AND INFLAMMATION	128
CARDIOVASCULAR	116

The number of partnership deals by therapeutic area in 2017.

*Includes dermatology, gastroenterology, genitourinary disorders, hematology, musculoskeletal, ophthalmology, and respiratory

Source: Pharma Intelligence

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Aerial view of the Blacksburg, Virginia, area.

Southeast Biotech: Rising Tall in the Valley

A look at the booming life sciences scene in southwest Virginia and Raleigh-Durham and Winston-Salem, North Carolina—and the region’s advantages in location, talent, and funding compared to the more glamour spots up north

By Michelle Maskaly

“**W**hat the [hell] are you guys doing in southwest Virginia?”

That’s the response Josep Bassaganya-Riera, chairman and CEO of Landos Biopharma, which produces first-in-class oral therapeutics for autoimmune disorders, says he typically gets when he pitches his Blacksburg, Va.-based biotech to investors in hot spots like San Francisco and New York.

But Bassaganya-Riera, who

grew up in Europe and has lived in various places around the world, wouldn’t think about headquartering his company anywhere else.

“There are beautiful mountains and it’s a great place to raise a family,” he says.

The area, surrounded by lush green valleys and sky-high mountain peaks, is also home to what some might call the region’s secret weapon when it comes to many industries, especially biotech: Virginia Tech, where Bassaganya-Riera is the

director of the Nutritional Immunology and Molecular Medicine Laboratory at the school’s Biocomplexity Institute.

If you consider the university’s long history of standout engineering and science-related student programs in human and animal health, add in the abundance of resources being made available to professors and students to commercialize research, as well as the cultural collision of the data and science worlds, you have a breeding ground for biotech innovation.

To help foster that innovation, the Biocomplexity Institute of Virginia Tech was conceived in response to a major policy initiative that established biotechnology as a central area of economic growth for the state. Building on early successes in genomic sequencing, the institute quickly established itself as a leader in another emerging scientific field, the simulation of complex systems. According to its website, “today, the Biocomplexity Institute is answering challenges to human health, habitat, and well-being at a scale that would have been inconceivable only a decade ago.”

Fostering an ecosystem

Without the correct ecosystem, however, it could all be lost. That’s where the Virginia Tech Corporate Research Center (VTCRC) comes into play. The 230-acre park is located adja-

“The Biocomplexity Institute is answering challenges to human health, habitat, and well-being at a scale that would have been inconceivable only a decade ago.”

cent to the Virginia Tech campus and within close proximity to Route 81, a main thoroughfare that makes desirable healthcare-related cities in North Carolina, as well as the nation’s capital, just hours away.

Created in July of 1985, the first building was completed in 1988, and is now home to 33 single- and multi-tenant structures. An expansion on the northwest side of the park provides enough land to con-

struct 16 additional buildings. VTCRC is a for-profit, wholly-owned, private subsidiary of the Virginia Tech Foundation.

The center has the ability to work closely with the university’s teaching mission by identifying opportunities for classes to use VTCRC and its companies for projects, special studies, internships, cooperative education experiences, and on-site instruction.

VTCRC also assists with university research programs and initiatives that facilitate economic development activities throughout the university by matching the needs of VTCRC businesses, facilities, and programs with the research and professional capabilities of Virginia Tech, helping to increase the level of industry-sponsored research at the school.

Much of the credit for the research park’s success is given

to Joe Meredith, president and CEO of VTCRC. He, and his staff, work closely with each of the businesses to provide as many resources as possible. In fact, one of the most touted attributes mentioned during a recent media day event was VTCRC’s flexibility, especially when it comes to space, whether it be wet lab or office space. Meredith is known to “tear up leases” and start from scratch to help companies adjust to their needs and keep them

in the VTCRC, according to a number of entrepreneurs *Pharm Exec* spoke with.

Many of the businesses located in the park have roots that trace back to Virginia Tech, such as CELLINK, a 3D bioprinting company; CytoRecovery, a licensed technology that enables the recovery and testing of subpopulations of cancer cells in tumor biopsies; and TechLab, a full-service *in vitro* diagnostic product manufacturer.

The fact these companies have been encouraged to stay local has had a direct impact on the economic development in the region by helping to keep talent in the area and also recruit new talent to the region. Rob Day, chief operations officer of Blacksburg-based TechLab, is a prime example. Day, who has been with the medical diagnostics company since 2000, grew up about an

hour from VTCRC, and was faced with a tough choice when he first entered the workforce—leave the region for a job in his field or do something completely different.

“After graduating from Virginia Tech, I had limited opportunities in the area at the time,” Day told *Pharm Exec*. “I worked for about five years locally with a cosmetics factory and was able to then find employment at TechLab. It was quite unusual at the time to be employed in microbiology and immunology in southwest Virginia. However, over the last 20 years or so, we have seen an incredible morph of the area and the biotech industry. ...I feel quite lucky to

Innovation Hub: At a Glance

SOUTHWEST VIRGINIA

Academics

» Virginia Tech, Radford University, Roanoke College, New River Community College, Hollins University, Virginia Western Community College

» Virginia Tech is a top 25 public research institution

» Virginia Tech has more than \$515 million in research expenditures

» SmartAsset named Virginia the No. 1 state for higher education in its third-annual ranking in March 2017

Unique partnership

» The Virginia Tech Carilion School of Medicine and Research Institute (VTCRI) public-private partnership. VTCRI creates a bridge between basic science research at Virginia Tech and clinical expertise at Carilion Clinic, and increases translational research opportunities for both partners.

Transportation

» Easy access to interstates 81 and 77

» Airports: Roanoke Blacksburg Regional Airport, Virginia Tech Montgomery Executive Airport

» Public Transportation: Amtrak, SmartWay Bus, Blacksburg Transit

Economics

» New River Valley was named a top 10 jobs market by *USA Today* in July

(Sources: <https://www.research.vt.edu>, <http://www.vtcrc.com>, <https://www.vabio.org>)

Innovation Hub: At a Glance

NORTH CAROLINA

Research Triangle Park

- » More than 3,000 patents awarded to RTP businesses
- » Largest research park in the country

Academics

- » Duke University, the University of North Carolina at Chapel Hill, North Carolina State University
- » Campbell University in Buies Creek offers a professional masters in clinical research as well as training in pharmacology
- » UNC's Eshelman School of Pharmacy tops national rankings and aligns its program of research with drug discovery and development cycles
- » UNC and NC State launched a joint biomedical engineering program. It includes regenerative medicine, tissue engineering, biomedical microdevices, pharmacoengineering, and drug safety.

Economics

- » More than 700 life science companies statewide, including 83 with foreign HQs, from 23 countries
- » 63,000+ workers in sector
- » More than 150 CROs based in state, employing 24,000 people
- » Third-largest biotech cluster in US behind California and Massachusetts
- » Total economic impact of life science industry exceeded \$86 billion in 2016
- » Industries invest more than \$296 million in R&D at the Triangle region's universities every year, double the average R&D investment of innovation clusters elsewhere in country
- » The 23.5% job growth in bioscience since 2001 is the highest among the 10 largest bioscience employer states

Transportation

- » Raleigh-Durham International Airport
- » Continuously increasing non-stop flights to popular domestic and international life science business destinations, including San Francisco, Boston, Paris, and London

(Sources: <https://www.rtp.org>, <http://raleigh-wake.org>, <https://www.rdu.com>, Colliers Research, centennial.ncsu.edu, CoStar Research, <https://www2.colliers.com/en>, NCBIO)

have found employment and been able to stay in this beautiful area.”

Location dollars

Southwest Virginia is visually about as far away from Kendall Square as you can get, and the people who live and work there are okay with that. In fact, area business development leaders are very transparent that the type of C-suite level executive you find in Blacksburg or the New River Valley would likely not be happy long-term in a San Francisco or Boston lifestyle.

The region gives those executives looking for a better quality of life access to world-class talent in a place they can do business without making a compromise. It's why, no matter the pushback he may initially get from investors, Bassaganya-Riera has no plans of moving his biotech, especially in the early years. “When a company starts out they are usually in bootstrapping mode and budgets are lean,” he says, a consideration that also makes southwest Virginia an appealing location due to its much lower costs to rent and buy space compared to Boston, for example.

Bassaganya-Riera finds that fundraising and networking is not impeded by being outside of the major biotech hubs, and that current-day technology allows him to bring and supply the resources he needs virtually.

But not everyone shares his opinion. Ed Champion, president of Roanoke-based Altede, a biotech whose work centers around food allergy-testing technology that was developed at Virginia Tech, and others told *Pharm Exec* that raising capital is an issue for them, because it is the one missing piece of the biotech ecosystem puzzle.

Local economic leaders, such as Brian Hamilton, economic development director for the Montgomery County Economic Development, and Charlie Jewell, executive director of Onward New River Valley, both acknowledge that the southwest Virginia area doesn't have the same financial ecosystem for biopharma companies as it does for technology companies, but that it can be

looked at as a chicken and egg situation. As biotech companies become successful and are acquired, it will naturally create a financial ecosystem as the founders decide to invest in other local companies.

Down the road

A few hours away from Blacksburg are the Raleigh-Durham and Winston-Salem areas of North Carolina. Like southwest Virginia, both locales are ripe for innovation in the areas of health and technology, given the

For some, raising capital is an issue in southwest Virginia, because it is the one missing piece of the biotech ecosystem puzzle

natural landscape of having Duke University, North Carolina State University, the University of North Carolina at Chapel Hill, and Wake Forest University all in close proximity.

Jack Bailey, president of US pharmaceuticals for GlaxoSmithKline, moved to the Raleigh-Durham area in the mid-1980s and has watched it transform into a biotech hotspot. Historically, there has been a good relationship between industry and the universities, creating a number of public/private partnerships.

“It's easy to do business here,” explains Bailey, adding that the cost of living is significantly lower than in other biopharma clusters and that the state government is very business-friendly. Bailey has been heavily involved in the region's life sciences initiatives and is proud of the work being done to make it a leader in biotech.

With direct flights to San Francisco, as well as other major domestic and international cities, executives who move to the area can find affordable homes, are two hours from the beach, two hours from the mountains, and are never at a loss for talent, Bailey says. Another aspect that makes the area attractive is the number of contract research organizations (CRO) that are headquartered here. For



Jack Bailey

early-stage drug developers, having direct access to CROs is very beneficial.

The talent game

The scientific talent coming out of the area universities is strong, but as Bailey and other pharma leaders explain, there is a concentrated effort to make sure there is enough executive-level support to help these young companies.



Cynthia Schwalm

Cynthia Schwalm, who was featured on the cover of *Pharm Exec's* September 2017 issue when she was the executive vice president and president of North American commercial operations for Ipsen, recently relocated from New Jersey to Raleigh-Durham.

“I feel like I am in the right place at the right time, because [the area] has all the right ingredients,” says Schwalm, who now serves on the board of di-

rectors for G1 Therapeutics, a clinical-stage biopharma company located in Research Triangle Park focused on the discovery, development, and commercialization of novel treatments for cancer. “There are brilliant biotech and life science companies popping up left and right.”

Schwalm is also helping elevate the profile of the annual Council for Entrepreneurial Development's Life Sciences Conference, which attracts nearly 1,000 worldwide attendees, including entrepreneurs, corporate leaders, and investors. The event, which will be in its 28th year in 2019, has been an important factor in putting the region on the map, especially in bringing in new financial opportunities for local startups.

Money, money, money

Although every entrepreneur would like more funding, when it comes to life science venture capital in Raleigh-Durham, it's not as much of an issue as compared to other areas of the southeast.

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Downtown Winston-Salem has become a hotbed for science and technology.

Following her career as a clinical scientist, Christy Shaffer, today the international project leader and associate director of pulmonary and critical care medicine at Burroughs Wellcome Co., joined Inspire Pharmaceuticals in 1995 as its first full-time employee. She was re-

“We don’t have as much venture capital as we’d like to have, but we have a couple strong firms known for working with these young, blossoming companies,” says Shaffer of the Winston-Salem area.

Meanwhile, other venture capital firms from across the country are noticing. While these companies may not have an office in the area, they are investing their money in local biotech companies, and many times, according to Shaffer, are returning more than once.

“Ten years ago, people who wouldn’t come to the region, because it meant two flights from the West Coast, are now moving to North Carolina because they see the vibrant [life sciences] ecosystem,” says Shaffer. “One of the things we do well, unlike San Francisco, is that we are all very collegial, and not as competitive. We see helping the ecosystem as helping us all out [long-term].”

No financial borders

The booming life sciences industry has helped give life to areas of North Carolina that otherwise might have seen an economic decline, like the Winston-Salem area.

“If you would have told me 15 years ago when I stepped foot on the campus of Wake Forest University that I would still be living here, I would have laughed at you,” says Will Partin, senior director, development at Wexford Science & Technology, which partners with institutions to create mixed-use, amenity-rich communities in knowledge-based locations. “When I started in this role in August 2011, within four blocks of where my office currently is, there were zero people working,

and there were maybe 30 condos and about 30 apartments. Fast forward to today and four blocks from where I am standing, there is a \$1.2 million historic redevelopment happening and over 3,500 people a day are working right here.”

Much of that growth has spawned out of the Wake Forest Baptist Medical Center’s decision to build properties in Winston-Salem. No one knows that better than Anthony Atala, chair and director of the Wake Forest Institute for Regenerative Medicine (WFIRM), which is located in the Richard Dean Biomedical Sciences building, anchoring the Piedmont Triad Research Park.

“The biotech ecosystem has changed dramatically,” Atala says. “Several years ago, the park evolved into what is now known as Wake Forest Innovation Quarter, a highly interactive science and technology-based community that has added to the revitalization and growth of Winston-Salem’s downtown.”

Wake Forest Innovation Quarter, located in Winston-Salem’s business district and centered in the North Carolina technology corridor, is one of the fastest growing urban-based districts for innovation in the US, according to Atala.

The executive, who travels all over the world sharing WFIRM’s science, says its location in Winston-Salem doesn’t limit the institute financially.

“Boston and San Francisco have a higher density of venture fund firms and investment banks; however, we have experienced no disadvantages being here, as these entities are willing to fund work without geographical limitations,” says Atala. **PE**

sponsible for raising over \$300 million for the Durham-based startup, including taking the company public in 2000. As president and CEO, Shaffer grew Inspire from 20 scientists to nearly 250 employees, with revenues of over \$100 million.

In 2010, Shaffer retired from her post at Inspire, a year before the company was acquired by Merck & Co. She joined Hatteras Venture Partners, based in Durham, in 2011 as the managing director of Hatteras Discovery, and became a general partner in 2016.

MICHELLE MASKALY is Pharm Exec’s Senior Editor. She can be reached at michelle.maskaly@ubm.com and on Twitter at @mmaskaly

Biopharma Business Check

Opportunities and obstacles have characterized 2018 to date

The increase in new drug approvals and candidates in development are good signs for pharma and biotech, but both sectors face continued pricing, cost, and healthcare policy-related challenges ahead

By Peter Young

2018 has turned out to be an exciting and challenging year for the pharmaceutical and biotechnology industries.

On the positive side, the number of new drugs approved and under development has escalated for both pharma and biotech companies. Pharma development productivity was weak for a number of years, but there has been a very visible increase in clinical success for a number, but not all, of the large pharma companies as they have adjusted their approach to development. Biotechs, as a group, continue to demonstrate their positive drug development capabilities.

The emergence of a host of new methods, such as immuno-oncology, CRISPR, personalized medicine, and stem cells has been promising, albeit with the normal periodic setbacks such as the one we are seeing in CRISPR. In addition, there have been many proposed and implemented changes in US FDA and Chinese FDA policies with regard to drug approvals that are favorable. Time will tell if the actual results match the intent.

As we will document in this article, biotech companies have been able to raise considerable equity capital through private placements, IPOs, and secondary public offerings. There has never been such a long period when the IPO window has been open for biotech companies as we have seen for a number of years now.

But the challenges are also visible as well. For the pharma companies, the challenges include low sales growth relative to history, the high cost of drug development, controversies around pricing, the scrutiny of orphan-drug pricing, lower profitability relative to history, increasing price and formulary pressure from payers, weak pricing leverage outside the US, and structural changes in healthcare and government policies in large countries such as the US and China that are impacting pharma. Biotech companies are facing some of the same challenges.

The rest of this article will look at what happened from an M&A, stock market, and financing point of view through the third quarter of 2018 and what we expect in the future. We will also comment on the implications of these trends for senior executives and investor decisions in the pharma and biotech industries.

Pharma equity market performance

During the first three quarters of 2018 the US equity markets were robust, with the S&P 500 increasing 8.1% while European markets were tepid, with the FTSE 100 decreasing by 1.8%.

The performance of the pharma and biotech industries varied dramatically by geographic region, company type, and sector.

The Y&P US Pharma index did well, increasing by 11.1%, while the European Pharma index was nearly flat, decreasing by 0.5%. The weaker European index performance was heavily influenced by the weak European stock market due to a variety of issues such as Brexit and the problems in certain countries such as Italy.

The Y&P Generic Pharma index also did poorly, decreasing by 5.5%, driven by accelerated abbreviated new drug application (ANDA) approval times, an increase in low-cost competitors from India and China, and hurdles to raising prices.

In contrast, the Y&P Specialty Pharma index did well, increasing by 17.8%, after a disastrous 2017. This improvement was not so much because the sector did well as it was a recovery from very negative sector events last year.

Pharma equity financing and M&A

Equity issuance in pharma has always been modest relative to the size of the industry. In the first three quarters of 2018, \$18 billion was raised, versus \$7.6 billion for all of 2017, a very significant increase on an annualized basis. In addition, during the same three quarters there were 11 pharmaceutical IPOs.

On the M&A front, during the first three quarters of this year, only 12 deals were completed worth \$18 billion, versus 23 deals completed worth \$42.1 billion in 2017. On an annualized basis, this was a dramatic decrease in terms of the number of transactions and dollar volume. Compared to many years of historical data, this level is also relatively modest.

As of September 30, 2018, the pipeline of the deals announced but not closed was \$93.9 billion (11 deals), with the Takeda acquisition of Shire dominating, accounting for \$81.7 billion of the total. The Shire deal aside, the pipeline was only \$12.2 billion.

Why the slowdown? It is partly due to a number of uncertainties facing the industry, but it is also due to a resurgence in the R&D productivity of many pharma companies, their recognition that the mega mergers did not accomplish much other than cost synergies, and a flood of biotech partnering and M&A transactions. The Takeda-Shire combo is a bit different because it is a major geographic move on the part of Takeda so that it will be less dependent on the Japanese market. The deal is still under antitrust review in the EU, so whether it goes through and when is not yet clear.

Biotech equity market performance

The performance of biotech shares were positive across the board during the first three quarters of this year. The Y&P Large, Mid, and Small Cap Biotech indices performed well, increasing by 7%, 19.4%, and 47.8%, respectively. This was a continuation of the positive performance of the sector last year.

Although part of the positive showing was driven by the

strong overall stock market, other factors were the solid business performance of many biotech companies, the emergence of new technologies, and indications by senior Washington officials that the FDA drug approval process is going to be accelerated. These positive trends were partially offset by the negative impact of the drug pricing issue and signs that orphan drugs will not get a free ride with regard to pricing.

Biotech equity financing and M&A

Biotech equity issuance in the first three quarters of 2018 totaled 200 offerings worth \$21.7 billion. On an annualized basis, it is on a pace to shatter the record dollar amount and number of issuances set in 2017, when \$21.1 billion was issued from 204 offerings.

Fifty IPOs were completed in the first three quarters, valued at \$4.9 billion. This number is already greater than the totals for 2017, when 44 IPOs equaling \$3.9 billion were completed, and on an annualized basis is approaching the 2014 record of 72 IPOs that raised \$5.7 billion.

Biotech M&A activity has almost always been modest historically, with small spurts of activity from time to time.

However, the first three quarters of this year saw a record dollar volume of \$31.4 billion, based on the value of the 24 biotech M&A deals completed. The number and the dollar value of biotech deals have gone up considerably. This was a significant increase on an annualized basis compared to 2017, when 24 deals worth \$15.1 billion were completed.

The increase has been driven by the strong demand for new drug products by pharma companies. It is somewhat unusual in

that biotech M&A is often weaker when the biotech IPO market is strong and biotech companies can postpone a sale of the company until further progress has been made. Obviously, the large pharma firms are willing to pay up to get at certain therapeutic areas, technologies, and pipelines.

The three largest deals were Celgene's acquisition of Juno Therapeutics for \$10 billion, Novartis' purchase of AveXis for \$8.1 billion, and Sanofi's acquisition of Ablynx NV for \$4.1 billion.

The dollar value of the pipeline of deals as of September 30, was solid, but not spectacular at \$3.5 billion (six deals).

Outlook: Pharma

Business. The business outlook for pharma companies is positive overall, but is a mixture of positives and negatives.

With regard to drug development, many pharma companies have promising, innovative drugs in their pipeline. The industry's trajectory with regard to drug development and productivity has been improving, both in-house and indirectly through the biotech industry.

However, there are many industry uncertainties that are evolving with regard to pricing, industry structure, the lower value of big pharma's sales forces and distribution to the biotechs pursuing orphan drugs, and ongoing patent expirations.

Generic pharma companies are under severe profit pressures and will continue to consolidate through mergers, cut costs, and try to push selectively into higher value and more protected product areas. They are under intense pricing and competitive pressure.

Specialty pharma has been partnering, in-licensing, and ac-

quiring to maintain growth and the strength of their overall business portfolios, but the business models of many of these companies are failing.

Equity markets. The stock market prices and valuations of the ethical pharma industry companies will continue to do well in the US, but with mixed results in Europe. The specialty and generic pharma company share prices will continue to suffer as these companies deal with serious business issues/pressures. It is our expectation that the negative news will continue to counterbalance the positive news for these two sectors of the biopharma industry.

Equity financing. We expect the equity financing market for pharma to be modest, but very healthy. The pharma industry tends not to raise new equity very often unless an individual company has to raise equity to repair their balance sheet after an acquisition.

M&A. Young & Partners expects M&A activity to continue to be subdued for the reasons mentioned. At the same time, the need to fill the shrinking drug pipeline will also fuel in-licensing arrangements, partnerships, and joint ventures with biotechs and other pharma companies.

Outlook: Biotech

Business. The development capabilities of biotech companies have been and will continue to be positive overall. Although there will be successes and failures by individual companies, biotech organizations have demonstrated their ability to develop new drugs at a faster pace than the larger pharma firms. There is also the hope that novel drugs and arrangements

with payers will allow biopharma companies to achieve attractive and sustainable pricing.

Equity markets. The stock market performance of biotechs has been volatile, but has been positive overall due to industry dynamics and a strong stock market. Overall performance will continue to be positive, driven by the net positive view of the biotech industry and its ability to produce new drugs.

Equity financing. Secondary equity offerings have been exceptionally strong and will continue to be solid, and IPOs will also perform well as long as the overall stock market environment is positive.

M&A. We believe that the biotech M&A market will continue to be strong both in terms of the numbers of deals and the dollar volume for the rest of this year and into next year. We expect the need for new drug candidates and revenues will drive pharma organizations to pursue biotech company acquisitions, in spite of the lofty valuations and the easy access to capital that the biotechs are enjoying currently.

However, their interest will be focused on specific targets in favored therapeutic and technology areas and/or on biotechs that have made significant clinical progress.

Implications for senior management


For ethical pharma firms, there will continue to be a wide variety of tools to acquire revenues and pipeline drugs, but the valuations will remain challenging, particularly for companies with promising drugs in late-stage clinical trials or in FDA approval. The challenge will be to pick the right overall mix of M&A, licensing,

and partnering to accomplish corporate strategic goals and defend and deliver shareholder value.

For specialty pharma companies, the key will be a rethinking of their strategies, since it is not clear that the pursuit of niche and orphan-drug markets will continue to bear fruit in the same way that they have in the past. The high price of acquisitions and the pressure on drug pricing even for orphan drugs will have a disproportionate impact on specialty pharma companies.

Generic pharma companies will continue to face a number of industry challenges. This will result in a continuation of the current industry consolidation and selective strategies around diversification. The CEOs of generic drugmakers must be prepared to shift to very different strategies to survive and to thrive.

For biotech companies, public and private, the future is exciting from the drug development side in terms of the approval environment and innovation and the improvement they have seen in the IPO, secondary equity financing, and M&A markets. However, prosperity or disappointment will vary by the story of each company. Unfortunately, the markets have been volatile and have played favorites with regard to therapies, technologies, and stages of development.

The key for biotech companies will be to properly assess their cash-flow requirements and to create and execute a flexible financing/M&A plan that properly assesses how much capital and at what cost of equity the various alternatives will provide, whether it is private placements, partnering, IPOs and secondary offerings, royalty monetizations, or sources of non-dilutive financing. 



PETER YOUNG is President and Managing Director of Young & Partners, a life science and chemicals investment banking firm, and a member of *Pharm Exec's* Editorial Advisory Board. He can be reached at pyoung@youngandpartners.com



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2008 ▶ Opening of El Kendi factory.



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ALGERIA

PRESSING AHEAD

Given Algeria's strong dependency on hydrocarbon export receipts, it was perhaps inevitable that the 2014 global oil price collapse – which halved the nation's foreign currency reserves, provoked a yawning budget deficit of more than 15 percent of GDP and crimped the government's ability to sustain costly subsidies – would ultimately impact the country's budding life sciences sector as well.

"The brute fact is that, as a nation, we had not been earning what we used to and that meant there were a lot of things that we suddenly found that we simply could no longer afford," reflects Senator Louise Chachoua, chairwoman of the congressional health commission, pointing to the overnight shelving of plans to construct five brand new, state-of-the-art University Hospitals (CHUs) and the shuttering of an eye-watering USD 262 billion 2015-19 public healthcare infrastructure renewal program.

Indeed, over the past five years, Algeria's life science space has been buffeted by a whirlwind of changes including: the nomination of a new technocratic-minded Health Minister in the form of ENT practitioner, Mokhtar Hasbellaoui, the enactment of a historic and transformative "sanitary law," the sudden and unexpected imposition of sweeping pharma and medical device import restrictions and much more besides.

"I think it's fair to say that we've witnessed some profound changes and a reshuffling of the rules of the game in the pharma and medtech sectors that have produced a new set of winners and losers," analyses IQVIA country manager, Hocine Mahdi. "While this USD 3.8 billion pharma market is still enjoying a growth spurt, it is revealing

that much of that new growth is nowadays accounted for by generics," he muses.

Nevertheless, for all the recent upheaval, the Algerian marketplace remains a high priority for MNCs investing in the Middle East and North Africa (MENA). "Algeria stands out as the jewel in the crown so to speak, not only because it is one of the most manifestly stable countries in an increasingly volatile region, but also due to the favorable population dynamics, sheer market size and the underlying reality that consumer demand continues to blossom," explains Essam Farouk, president of El Kendi.

Haissam Chraiteh, Sanofi's managing director, very much concurs. "From a business point of view, Algeria has a great deal to offer. Not only is this the second largest market on the African continent, but it is also a heavyweight when compared to the Middle Eastern markets. One of the characteristics that immediately stands out in Algeria is the sheer importance that the authorities place on securing access to healthcare for patients. This is rather exceptional within the region. Algeria is one of the only countries where care is provided universally and covered by the state. Also distinctive is the maturity of the local healthcare infrastructure. Because of a robust contextual environment, enterprises like Sanofi are able to generate more of an impact than would otherwise be the case," he confides.

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“Nor should one forget that the scope of medical coverage is exceptionally high, reaching some 85 percent of the entire 38 million population,” ventures Loic Galmard, the recently appointed general manager of Janssen. “This is not at all common in African countries, which are almost always characterized by high co-payment health systems whereby the patient must pay for treatment out of their own pocket,” he adds.

A MILESTONE HEALTH REFORM

One very exciting development has been the securing of parliamentary approval in August for a wide-reaching healthcare law (“Loi Sanitaire”), the first such bill since the 1980s, which strives to render the nation’s public healthcare apparatus fit-for-purpose in an era when the patient population has been ballooning and incidence of non-transmissible chronic, lifestyle disease such as diabetes and pulmonary arterial hypertension are undergoing a sharp rise.

“This really is a watershed moment, not just because of the myriad of well thought out articles in this legislation that will help to modernize and bring up to date our healthcare system, but also because it is an organic and flexible document that empowers the Ministry of Health to make subsequent amendments through implementing decrees,” details Farid Benhamdine, president of the Algerian Society of Pharmacy.

One key thematic being pursued is the reorganization of care pathways. “We seek to enhance permeability between the public health institutions of proximity and the hospitals, by mutualizing equipment, human and financial resources and entrusting the management to a single entity, as is the trend globally. In Algeria, this should translate to a better distribution between a Health Unit of Proximity (USP), the general hospitals (HG), and the specialized hospitals (HS),” reveals Mohamed L’Hadj, director general of health services and hospital reform.

These efforts go hand in hand with concerted attempts to professionalize hospital management and optimize core activ-



Louisa Chachoua, president, health commission at the Senate; Mohamed L’Hadj, director general of health services and hospital reform; Djaouad Braham Bourkaib, director general of social security

ities such as procurement to make better use of the resources available. “The moment has come when we need to start thinking outside of the box and prove ready to embrace more enlightened methodologies for how we go about the day-to-day task of delivering healthcare,” urges Minister Hasbellaoui.

Unsurprisingly this is music to the ears of the international drug developers who are acutely aware of the importance of generating efficiencies so as to free up more funding for financing innovative therapies. “I think I speak for all of my peers when I say that bioMérieux resoundingly welcomes this step... the bottleneck today is the two divergent leadership styles in charge of Algerian hospitals: strict business managers with little appreciation or understanding of the workings of the life sciences sphere or physicians with the requisite scientific know-how, but not the fundamental managerial nous. Ideally, we should be trying to cultivate a new cadre of professionals well-versed in both skill sets,” suggests the French firm’s area business manager for the Maghreb, Nadia Oka-Bousbia.

Interestingly, bioMérieux is now looking to partner with the Algerian authorities in an attempt to somewhat plug this gap by leveraging the company’s links with its Mérieux Université to provide professional development training for healthcare practitioners. “The Mérieux Université is a 40-year old center for collaboration and training for Institut Mérieux companies that is also open to external companies and institutions. The purpose is essentially to develop talent, improve organizational efficiency and entrepreneurial leadership, as well as to promote a culture of excellence within the life science and healthcare space... Already we offer such services on a small scale to some of our private lab customers and are exploring ways to expand this out into the institutional setting. So far, the Ministry has proved to be highly receptive to such a concept,” explains Oka-Bousbia.

TWEAKING THE REGULATORY RULEBOOK

At the same time, Algeria’s social security apparatus has been pulling out all the stops to devise fresh mechanisms through which patient access to latest generation, sophisticated medicines can be secured without jeopardizing the long-term financial viability of the public health apparatus.

TOP 10 PHARMA COMPANIES IN ALGERIA

Source: IQVIA

Sales for 2017 (USD millions)

1	SANOFI	458.6
2	EL KENDI	254.1
3	NOVO NORDISK	239.1
4	HIKMA PHARMA	167.3
5	GLAXOSMITHKLINE	150.6
6	PFIZER	112.3
7	MERINAL	104.4
8	SAIDAL	85.0
9	PHARMALLIANCE	84.9
10	BEKER	79.3





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Nadia Oka-Bousbia, country manager Algeria & North Africa, bioMérieux; Amine Sekhri, country manager, Roche; Loïc Galmard, country manager, Janssen; Doria Oughlis, general manager North West Africa, Lilly

“We needed to formulate and define another set of rules that may be slightly more complex, but in exchange we will open rationally the access to innovative drugs and will share with pharmaceutical companies a financial risk and prevent budgetary drift. From now on, we will be able to imagine contracts based on price and volume with an annual expense limit,” recounts Djaouad Braham Bourkaib, director general of social security at the Ministry of Labor. “Furthermore, we are starting to offer performance-based contracts as a way of delivering access to innovative drugs where the medical risk is not covered,” he proudly confirms.

Such a move would certainly represent a significant step forward but putting in place these capabilities is no easy task. “There is an entire arsenal of managed entry tools that incorporate risk sharing and pay-per-performance elements that could potentially be harnessed to eke more value out of the financial resources being deployed, however, most of these solutions presuppose a functioning Health Technology Assessment (HTA) mechanism, data collection and IT infrastructure so as to be able to track and measure mission fulfilment. We all know that slashing prices is not the best way to achieve effective public health provision, but the authorities will point out that they have few ready-made alternatives to turn to, so the onus is on companies like us to help them mature their embryonic HTA apparatus as speedily as possible,” concedes Roche’s country manager, Amine Sekhri.

Janssen’s Loïc Galmard voices very similar concerns about the shortcomings of the current setup. “Though we detect a strong desire on the part of the authorities to introduce HTA methodologies to be able to gain better visibility around the value and performance of specific biologics, the existing data collection and processing capabilities are generally insufficient. For example, currently no one really knows how much it costs for a patient to receive one day of treatment for prostate cancer or for schizophrenia in an Algerian hospital and that, in turn, makes it very difficult for companies to compile pharmaco-economic evidence and calculate how a specific drug can generate savings,” he warns.

That said, the state machine has slowly but surely been bolstering its capabilities. Social Security is in the midst of putting in place a medical big data system to afford greater visibility in real time of the results of the contracts; a new regulatory body, the National Agency for Pharmaceutical Products (ANPP) has been established as a counterpart to the National Laboratory for the Control of Pharmaceuticals (LNCPP); and pilot programs have already been launched in the cities of Sétif and Oran, where some 17 percent of polyclinics are now using digital medical records.

Decision making by the payer has also become noticeably more discerning. “Sometimes we also ask for drug efficiency to be tested every six months, or for reimbursement to be re-approved periodically. For instance, some patients develop resistance to the medication and no longer benefit from Interferon beta drugs – used in multiple sclerosis as disease-modifying drugs in the hope of reducing the frequency of relapses and slowing the progression of the disability. The thing is that these drugs are very expensive, so we want to verify together with healthcare professionals and be certain that the patient is still benefiting from the treatment before continuing to pay for something useless” reveals Bourkaib. Greater scrutiny can equally be witnessed in the fact that positive reimbursement



The “Cancer Plan”: A Sandbox for Experimentation



**Messaoud
Zitouni, head,
Cancer Plan**

While Algeria has been making clear headway in the war against cancer (rates of fatality for colorectal cancer have decreased by half within only five years, and patients with metastasized lung cancer are now living three times longer than previously), the country’s much-acclaimed National Cancer Plan has also been winning plaudits for transforming Algerian healthcare. “Strategically, we can say that the Plan in itself has been something of a role model for the country and showcases what could potentially be achieved in other therapeutic areas. Born out of a crisis around the obsolescence of radiotherapy centers back in 2009, we have unexpectedly managed to use the initiative as a vehicle for redefining treatment pathways,” reminisces the program’s director, Professor Messaoud Zitouni.

The American biotech, Amgen, for example, has been partnering with the authorities to introduce biomarkers. “We equipped the Mustapha Pasha hospital with advanced equipment and training in the discipline of next generation sequencing of cancers. This ultimately helps personalize diagnoses, and provides access to targeted therapy, and better prescribing of drugs... Our products are expensive, so we want them to be used properly on the correct patient and the correct diagnoses,” recounts Radwa Terbeche, the Algerian affiliate’s general manager.

Roche, for its part, has been at the forefront of establishing a national cancer registry and is playing an active role in developing accreditation of the cancer research centers through PACT program. “Putting in place the register has been absolutely fundamental because it helps extrapolate the data necessary to understand the dynamics of cancer in the country and demonstrates the possibilities for personalized care that are opened up by mixing science with data. This is precisely the sort of game-changer that may one day enable Algeria to leapfrog forward and accelerate its development path in life sciences,” argues Roche’s Amine Sekhri.



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SANOFI
Empowering Life



Ismael Chikhoun,
president &
CEO, US-Algeria
Business Council
(US-ABC)



Malika
Benmouffok,
country
manager, Tabuk
Pharmaceuticals

decisions are now increasing tied to specific indications with a proven improvement of medical service rather than issued as blanket approvals for treating multiple illnesses.

Innovative drug producers with best-in-class products, meanwhile, tend to be more than happy to enter into such agreements in return for ensuring that their therapy actually reaches the market. “As a company, we are very sensitive to the needs of the state apparatus to make the national health system more financially sustainable. We therefore put much thought into bringing products to the market that can help take costs out of the system and achieve better pharmaco-economic performance,” posits Doria Oughlis, general manager for North West Africa at Lilly.

She points to her company’s osteoporosis solution, Forteo®, as the type of win-win transformative treatment that could be introduced through a bespoke access agreement. “Though the face value of Forteo® might be higher than some of the rival treatments available, the fact

that this osteo-former helps restructure and reconstitute the bones that have been thinning and thus prevents fractures means that considerable cash savings are generated through the lack of a need for future surgeries and hospital visits... This therapy can therefore serve to alleviate pressure on the state apparatus and achieve genuine value for money over the long run, which is why we are currently in negotiations with the Central Pharmacy for Hospitals (PCH) to agree upon an appropriate formula for accessing Algerian patients,” she reasons.

INDUSTRIAL POLICY: STRONG-ARM STRATEGIES

While efforts to build an HTA infrastructure have been roundly applauded by international drug developers, Algeria’s overtly protectionist pharmaceutical manufacturing policy has long proven troublesome for their operation. “Importing life science technology into Algeria can certainly pose quite a challenge: The amount of time taken to secure customs clearance is generally around six weeks compared to a two-week average in the region and this applies to both finished products and spare parts,” explains bioMérieux’s Nadia Oka-Bousbia.

However, the Algerian authorities justify such policies in the name of cultivating their own industrial drug fabrication base. “One of our core mandates and socio-economic responsibilities is actually to promote and foster domestic manufacturing of drugs, both by indigenous Algerian outfits and international companies that have settled in Algeria, and, to this effect, our reimbursement policy explicitly privileges homegrown therapies,” counters Djaouad Bourkaib of the Social Security.

Matters reached a crescendo in the summer of 2017, however, when the Algerian Ministries of Trade, Finance and Industry, unexpectedly imposed sweeping import restrictions on any incoming pharmaceuticals and medical devices for which there was some sort of domestically manufactured substitute, ostensibly with a view to preventing currency flight at a time when the national economy was deteriorating. “The episode was frankly emblematic of the type of risks that foreign businesses can run into and which can render it difficult to stick to long-term business strategies,” exclaims the US-ABC’s Ismael Chikhoun. “I personally believe the government would have done far better to have consulted with the industry first, because quite a large number of foreign enterprises unfortunately found their business models invalidated practically overnight and if there is one thing that is almost certain to scare off potential investors, it is an uncertain operating environment where there is little or no predictability,” he reflects.

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Our therapeutic areas





Algerian Manufacturing: Stepping up into the Big League



Haissam Chraiteh,
country chair,
Sanofi

No pharma MNC has been more willing to invest so deeply in Algeria than long-time market leader Sanofi. “A few years ago, we decided that, after a few years of sustainable growth, the time was ripe to invest in a high-grade industrial complex capable of manufacturing different forms all the way up highly sophisticated products. The new six-acre facility is earmarked to manufacture more than 100 million units per year with an investment of over EUR 85 million (USD 98 million).

When officially opened in October 2018, the factory will rank as the largest industrial complex of pharmaceutical produc-

tion and distribution in Africa,” proudly reveals the Algerian affiliate’s managing director, Haissam Chraiteh.

The French multinational already owns two existing production plants – one located at Oued Smar specializing in solid forms, and another in Ain Benian dedicated to liquid forms. Chraiteh notes that Sanofi’s “continuous investment in local production will considerably enhance our capacity for local manufacturing and thus ensure domestic availability and security of supply of our products in large volumes.”

He concludes, “All in all, this is a great statement of Sanofi’s long-term engagement in Algeria for patient welfare. Furthermore, with the support of authorities, this industrial complex will also be able to develop new forms and new ranges of products in the future.”

The experience of Tabuk Pharma is perhaps illustrative of the conundrum facing many MNCs. “There is no denying that this was an especially difficult period for the local affiliate,” remembers Malika Benmouffok, the company’s country manager. “Prior to the sudden importation ban we were on a very good growth trajectory and had been registering an annual turnover of around USD 20 million, but, in one fell swoop, our revenues took a nosedive. Then, in July, there was some relaxation in the regulations and we were granted a quota on cephalosporin imports because local manufacturers were failing to cater to the full demand of the domestic market. Nevertheless, despite this slight respite the situation remained challenging for us, because cephalosporin antibiotics accounted for some 70 percent of our imports and we realized we were going to have to change tack if we were to deliver on our targets of entering the top ten companies by sales value by 2023,” she confides.

Tabuk’s leadership ultimately calculated that the logical way out of this impasse would be to adapt the business model and orientate more towards local manufacturing. “My global management board answered quickly to the Algerian economic situation by committing to invest in manufacturing and made the leap in good faith for the good of the Algerian patient... We have thus resolved to produce cephalosporin antibiotics in dry form from our existing in-country facility at Blida and will be targeting a potential of 20 million packs or more per year to maintain our intended profitability,” she confirms.

“We respect and follow the political decisions that are taken for the good of the country and are sympathetic to the authorities’ agenda: at the end of the day, they are the sentries and guarantors of the public health of the nation and we admire the way they are endeavoring to strike a balance between economical constraints, patients’ needs, administrative and production delays and industrial realities,” insists Benmouffok.

Many MNCs keen to protect their market positioning thus find themselves being compelled to engage in some form of local production. “Given the sheer intensity of the protectionism that we

are witnessing, there are clearly considerable incentives to investing deep into the market and establishing in-country manufacturing capabilities. The way I interpret it, firms stand to gain a lot from embarking down this path and conversely have much to lose if they do not,” analyses Janssen’s Loic Galmard.

“You can almost divide the multinationals into three baskets: those that prepared their localization strategies years ago and are now benefiting from early mover advantage; those that are coming late to the process and are scrambling to restructure their business models; and those that are still too timid to establish a local production footprint and risk becoming ever more marginalized to the extent that they may even find themselves locked out of the marketplace altogether,” surmises IQVIA’s Hocine Mahdi.



Guillaume Seillier,
director general,
Servier



Adlane Soudani,
president and
managing director,
Ipsen Pharma
Algerie SPA

One company that certainly did anticipate the need to invest in a facility was Sandoz. “The government’s zeal for rendering Algeria a pharma manufacturing powerhouse actually preceded the oil price decline, and dates back to a pre-2014 promise to ensure that at least 70 percent of national drug consumption could be met by in-country production, thus the sort of measures that came into force last year should not really have been a total surprise to anyone. The oil prices merely accelerated the pace of a project that was already well in motion. Consequently, as early as 2015, the Sandoz-Novartis group had already committed to investing some USD 35 million in upgrading our legacy facility in Oued Smar,” points out Mourad Ishak, the company’s head for North West Africa.



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“Essentially, we realized the inherent fragility of being too reliant on imports and hence struck upon a formula whereby Novartis Technical Operations (NTO) in Oued Smar would centrally manage our manufacturing operations across both our innovative medicines and generics divisions, with the goal of further improving efficiency. Nowadays, we locally manufacture a wide range of products in the cardio-metabolic therapy area including the Tareg®/Diovan®, Galvus® and Exforge® ranges. Moreover, the recent big-ticket investment to revamp the NTO plant will not just expand production capacity but install state-of-the-art technologies and equipment that open the door to producing high sophistication innovative medicines in-country,” concludes Karim Harchaoui, country manager of Novartis.

THE SCRAMBLE TO LOCALIZE

Embarking on a localization strategy is no small matter, however, especially if you are an innovative drug company with an international reputation to maintain. “While in-country manufacturing in Algeria is extremely developed for basic drugs, it is markedly less so for high potency products such as many oncology drugs. To overcome this, MNCs must invest heavily in technology transfer. There are essentially two alternatives: either you sign a commercial agreement, where a CMO is handed the opportunity to update their facilities and integrate fresh know-how and technology in the short to mid-term, or you invest directly in establishing your own plant in conjunction with an indigenous JV partner,” notes Janssen’s Loic Galmard.

Some companies, including Abbott, have calculated that they simply do not possess enough Algerian market demand to justify setting up our own proprietary manufacturing facility, so they opt for the contract-manufacturing pathway. “The limitation with third party manufacturing (TPM) is that you can only be in control of the entirety of the other parts of the value chain when the factory is registered under your name,”



Rachid Kerrar,
director general,
Beker



Essam Farouk,
president, El Kendi

explains the company’s general manager for Francophone Africa Cluster, Mohamed Benali Khoudja.

Identifying a suitable CMO partner can also be tricky. “Not all the 90 odd facilities in Algeria are GMP approved. There are some big players, such as Biopharma, but you also have a multitude of smaller players with questionable quality standards that would be way too risky to enter into partnership with. There are, at a minimum, ten to 15 sites that possess the requisite high-quality standards. They therefore tend to be keenly sought after by the MNCs scrambling to localize,” he points out.

IQVIA’s Hocine Mahdi very much concurs. “The handful of indigenous contract manufacturers that have managed to attain international quality standards are left holding the cards because they can choose from an unprecedented number of business proposals,” he observes.

That has certainly been the experience of Servier. “Back in 2012, when we first required the services of an Algerian CMO, there were very few players that matched our quality requirements and expectations and it thus took a long time to carry out the requisite due diligence. Nowadays overall standards are higher, and there are noticeably more options. The challenges these days are different. The auditing process is still critical since we have encountered many outfits claiming that they are ready for operations, but who will probably fail to deliver the required quality or quantity, because they have so many other alternatives, and perhaps more attractive, options at their disposal,” claims the general manager, Guillaume Seillier.



DIAGNOSTICS IS POWER

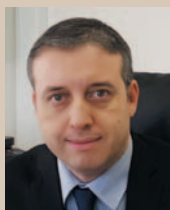
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All Aboard the Biosimilars Bandwagon



Sofiane Achi,
director general,
El Kendi

With the pharmaceutical import bill having almost topped USD two billion in 2017 mainly on the back of high price tag biologics, many industry insiders consider biosimilars to herald one of the most effective ways of containing costs without diminishing the quality of healthcare provision. “People nowadays understand the vital role that generics play in freeing up capital to spend on latest generation innovative therapies and exactly the same logic holds true for biosimilars as well... We believe greater biosimilars penetration will be a prerequisite for reducing the national drugs bill and for fashioning a financially stable public health system that can continue to deliver upon its objectives and, as such, we are staunchly committed to making this happen,” reflects El Kendi’s Sofiane Achi.



Radwa Terbeche,
director general,
Amgen

Amgen, meanwhile, has selected Algeria as one of its priority markets for launching biosimilars. “We will, for sure, be participating in the first wave of biosimilar products launched here... The normal time for registration from submitting the application to receiving permission is 24-36 months, although we are working to optimize these timelines. The beauty of biosimilars is that they offer a significantly more cost-friendly pathway to delivering latest-generation innovative medicine,” says the company’s general manager Radwa Terbeche.



A. Gharbi,
director general,
National
Laboratory
of Control for
Pharmaceutical
Products
(LNCPP)

The primary bottleneck up until now has, of course, been the absence of specific legislation for biologic-based products so companies like Amgen and El Kendi have been busily interacting with lawmakers and health officials with a view to helping prepare the ground for their eventual arrival. “As a responsible industry stakeholder, Amgen has been participating in consultations with the government on drafting a biosimilar regulation, providing international experts to these consultations to offer new perspectives so that we can implement suitable legal structures right from the start,” reveals Terbeche.

Already a momentum is clearly underway. “Rather than blocking access entirely the authorities have instead introducing more stringent legislation for new drug requirements, so there has been a work-around solution and temporary fix prior to the introduction of some kind of bespoke registration pathway which we are expecting to be published at some point in 2019,” she clarifies.

The regulatory apparatus has been busily trying to get up to speed. “We recently sent a team to Argentina to inspire us to establish an industry of biosimilars. The goal is a transfer of technology that will allow us to be up-to-date and to follow or even anticipate future developments in this area,” details Abdelaziz Gharbi, director general of the LNCPP.

El Kendi, meanwhile, is even evaluating different options about how to transfer part of the added value related to manufacturing biosimilars to its Algerian factories. “We want to enrich the debate and play our role in raising the awareness of the users, doctors, pharmacists, authorities, and patients. Two to three years ago, biosimilars carried a big question mark and seemed unrealistic. Nowadays there is a much better understanding and a clear roadmap going forward. El Kendi has positioned itself right at the vanguard and we seek to play a lead role in shaping the new environment,” declares Achi.

Opting to establish your own proprietary plant, however, carries its own challenges.

“There are a lot of parameters and variables to consider in a project like this above and beyond securing the requisite financing and the physical construction of the facility. One key consideration will be how to source the human capital needed to staff your site and then there is also the tricky matter of identifying an appropriate indigenous JV partner under the obligatory 49/51 percent ownership rules,” counsels Roche’s Amine Sekhri.

AHK’s Marko Ackermann is quick to point out the standard of potential local JV partners in Algeria is actually rather higher than many international investors’ expectations. “Typically, candidates are more interested in technology and know-how transfer than in pure financial investment which they are often easily able to source locally anyhow. In the pharmaceuticals sector their main objective is often to scale the manufacturing value chain and therefore to acquire the capabilities and the competencies to produce ever more complex molecules,” he notes.

In spite of the manifest complexities of developing a production footprint, many of the better-known pharma MNCs have not been deterred and have ultimately elected to take the plunge. Pierre Fabre’s managing director, Nawel Baba Hamed notes that the dermatology specialist launched a JV with Algerian partners in May 2018 for the commercialization and production of medicines. “It will operate under the 49/51 rule. The project will benefit from a EUR 15 million (USD 17 million) initial investment and we will produce several pharmaceutical forms (tablets, liquids...) with the aim of being able to produce the majority of our portfolio locally in the mid-term,” she assures.

Dar Al Dawa, meanwhile has committed USD 20-25 million for a plant that will include the manufacturing of eye-drops. “The output volume will depend on the number of products we manufacture. We already have 16 products being produced. The first one entered the market in August, following marketing authorization and, by

2019, we will manufacture between 30-40 products locally with the goal of releasing a new product onto the market every two months,” announces the general manager, Nouredine Issad.

Interestingly, the French oncology-focused midcap, Ipsen, stands out for pursuing both localization strategies concurrently. “It is quite a common trend nowadays within the Algerian market for international drug developers to begin by teaming up with a local CMO, before seeking to build up the infrastructure for independent local production, so, back in 2014, we formed an agreement with AT Pharma (Hydra Pharm Group), a credible domestic player that was responsible for the manufacturing of our flagship gastroenterology drug, Smecta® as our first stepping stone to full localization. Our rather distinctive approach, however, is to deploy parallel strategies: we will maintain our longstanding local partnerships, while, at the same time, expanding our footprint out into performing our own local production,” divulges the firm’s general manager Adlane Soudani.

“There is an expectation on the part of the authorities for incoming multinationals to invest materially in the country. We figured that investing in yet another facility producing classically synthesized molecules would not deliver any real value-add in terms of “know how” and tech transfer. Hence, we decided to bring innovation in the form of manufacturing Decapeptyl®.



Nawel Baba-Hamed,
general manager,
Pierre Fabre



Moncef Bouabid,
Algeria oncology
BU country head,
Novartis

This has several indications. The main one is for the hormonal treatment of locally advanced metastatic prostate cancer that can be now injected subcutaneously too. A plant dedicated to Decapeptyl® is bringing true innovation, and is a first for both Algeria and Africa. We will also continue to forge partnerships with local companies. We view it as important to deliver tech transfer to local companies, which will aid the development of the local industry and assist with indigenous efforts to scale the value chain,” he asserts.

Ipsen is particularly keen to be perceived as a true partner that is fully engaged and embedded in the socio-economic fabric of the host market. “It is imperative for us to deliver on the scale, and in the time frame that we promised,” declares Soudani. “Ipsen is keen to demonstrate that we walk the talk. Managing expectations on all sides is paramount.”




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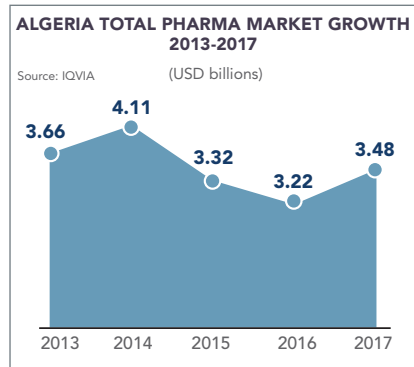
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FIT FOR EXPORT?

Barely a decade ago, Algeria was importing almost all of its pharmaceuticals, but thanks to the ever-greater state protection for local manufacturing and the way in which successive administrations have compelled the multinational drug developers to localize their production, the country can nowadays supply upwards of 50 percent of national drug consumption. Given all of that domestic capacity, the logical next step will be whether Algeria can successfully transition over to becoming a pharma exporter. “We are quietly confident that Algeria is well on the path to being considered a production platform and launchpad for exports into other parts of Africa and well beyond as we can lay claim to significant capacity, good quality and low prices,” affirms Rachid Kerrar, general manager of Algerian manufacturing outfit, Beker, which already has a fledgling export arm up and running. “I notice quite a few surprised gazes coming our way with regard to our recent move into exportation, but I truly believe this is a sign of things to come more generally,” he says.

The path to export, however, appears to be long and tortuous. The Algerian pharma manufacturing space needs to be better rationalized. For certain categories of drug or therapeutic area there is a surfeit of capacity and facilities are not running



to their full potential. In other areas there is not enough supply to meet demand. It's a mix of duplication and gaps. Greater export orientation would, of course, represent one way of alleviating this situation. El Kendi started production one month ago in a new facility. We have a massive spare capacity and we need to find a way to use it. In our calculation, the only way to work at full capacity would be to export – precisely the strategy that we have opted for,” contemplates Essam Farouk.

With products now being registered for export to no fewer than five Middle Eastern markets as well as to Europe, Farouk is conscious of El Kendi's responsibility as an ambassador and standard bearer for the “made in Algeria” brand, but believes that his company's own successes in broadening its horizons will be a tough act to follow for the rest of the local industry. “When exporting, it is critical


to have access points to other markets. Often Algerian companies do not possess this and thus struggle to make it onto the international stage. What's more, many home grown Algerian drug developers are family owned firms and tend to be reluctant to engage in the types of mergers and acquisitions required to develop the scale where they can export. Given that we possess sister companies abroad, for example in Jordan, should we seek to launch a product in Jordan, we simply must harness our local affiliate's apparatus to launch it. This is the beauty of the El Kendi business model which sets us apart from our peers,” he reasons.

BOOM TIME FOR ONCOLOGY

“Market access is always going to be noticeably simpler when you can manage to build a bridge to state health priorities: we already benefit hugely from our participation in the National Cancer Plan and feel this is a great opportunity for the local affiliate to establish a backbone in onco-hematology,” states Janssen's Loic Galmard.


Not surprisingly other big players have been tilting their portfolios in that direction. Pierre Fabre, for instance, has designated oncology as a focus area and is looking towards providing a comprehensive range of treatments spanning therapies for breast, lung, blood and

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¹ WHO. “Cancer: Key Facts.” <http://www.who.int/mediacentre/factsheets/fs299/en/>. Accessed February 2017.

² PM Live. “Top 25 pharma companies by oncology sales.” http://www.pmlive.com/top_pharma_list/oncology_revenues. Accessed February 2017.

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bladder cancers. “Year in, year out, our pharmaceutical division spends around 50 percent of its R&D budget on oncology, so it makes perfect sense that we start doing more in this area in Algeria,” explains general manager, Nawel Baba Hamed. “Our next step is to launch a new targeted therapy in melanoma. The European Commission has just granted marketing authorization for the combination of Braftovi and Mektovi for the treatment of adult patients with unresectable or metastatic

melanoma with BRAF mutation and our expectation is very much to launch in Algeria in 2020. We have already launched a local epidemiological study on melanoma,” she adds.

Novartis Oncology meanwhile has been pushing new boundaries by conducting oncology-focused clinical research within Algeria. “We are only the second company in the country to be engaged in this type of activity for this specific therapeutic area and that is testament to the on-going efforts of the standalone business unit... We are thus providing the opportunity to use our products with patients, at both second and third study stages,” discloses Moncef Bouabid, the Oncology BU country head. He even foresees a point in which his company will be able to enable Algerian patients to access sophisticated technologies like CAR-T. “The benefit of this therapy is that the treatment doesn’t require onsite provision. Instead the blood can be sent to the laboratory, modified in the laboratory, and returned to the patient. The challenge within the country will be about the monitoring and follow up treatments, but we are confident that this can be, at some stage, surmounted,” he reassures.

Projecting Influence



Zoubir Harrat,
director general,
Pasteur Institute
of Algeria

As the African continent inches towards pharma regulatory convergence with a roadmap already agreed upon to establish an African Medicines Agency (AMA) that shall promote the adoption and harmonization of medical products regulatory policies and standards, Algeria is widely expected to be readying its candidacy in a bid to host the new secretariat. “One very much gets the sense that our nation is gearing up to become a regional role model for life sciences. You only

have to look at the gathering momentum behind plans to base the Pan-African Super Regulator out of Algiers, to feel that we are finally beginning to step out of the shadows and assert ourselves,” suggests Lilly’s Doria Oughlis.

It would certainly appear that on multiple levels that Algeria is now starting to be more proactive in projecting its influence. “These days there is a concerted effort on the part of the state to assume more of a leadership position and contribute to multi-nation initiatives. Institut Pasteur has explicitly been trying to ramp up our activities across the Middle East & Africa axis by championing and mobilizing combined initiatives to fight and prevent regionally common diseases including Rabies, Leishmaniasis and mosquito-transmittable diseases,” affirms Zoubir Harrat, general manager of the Institut Pasteur.

Sanofi’s Haissam Chraiteh meanwhile recalls specialists from other North African nations visiting specifically to observe the rollout of mobile diagnostic vans for breast cancer screening and how “the country is fast-becoming a benchmark that neighboring health authorities will seek to emulate and replicate.”

“Algeria has forged strong relationships with other African states, so the groundwork is already in place. There is also the wealth of knowledge, and infrastructure, which renders the country well suited to a position of hegemony,” he adds, all the while noting that there will be strong competition from South Africa.

“Our nation definitely possesses the means, the wherewithal, and the human resource to lead others, but one country cannot carry such ambition on its own if there is not some sort of consensus across the region,” reminds Senator Chachoua, no doubt referring to North Africa’s longstanding failure to integrate and coordinate policy.

MAGNET FOR REGIONAL HEADQUARTERS

Interestingly, for all the idiosyncrasies of the Algerian marketplace, multinationals are increasingly choosing Algiers as a regional headquarters. “Algeria has traditionally not always been considered the obvious location for situating a regional office, but though a multitude of administrative and logistical hurdles remain, the logic for doing so is becoming ever-more apparent,” explains Doria Oughlis of Lilly.

“Firstly, the market is growing at a frenetic pace, which is certainly not the case in either Morocco or Tunisia or even much of Europe for that matter. As soon as you start to factor in the rapid population growth and the epidemiological shift, then the envelope of opportunity to get involved with this market is immense. Moreover, Algeria is also very much an outlier within its region when it comes to the willingness on the part of the state to engage in public private partnerships. The hard-nosed fact is that we don’t have PPPs on issues like patient and practitioner education in the other North West Africa cluster states and it is testament to the vision of the Algerian ministry of health that we are able to roll out such programs here,” she continues.

“Making Algeria the sub-regional hub has its advantages and disadvantages. Traditionally, many MNCs have regarded the comparatively open and liberalized economies of Tunisia and Morocco as more welcoming to foreign investment and more aligned with international norms so have preferred to place their headquarters there. However, we saw things rather differently,” recounts bioMérieux’s area business manager for the Maghreb, Nadia Oka-Bousbia. “The sheer size of the Algerian market, the volume of entrepreneurial opportunities and maturity of the public health system all render it strategi-

cally and commercially interesting and present a pretty compelling business case.”

Abbott’s Francophone Africa Cluster head, Mohamed Benali Khoudja has come to the same conclusion. “From a business standpoint, it’s a no brainer to build the greatest presence in the largest market, which, for us, is Algeria by quite some way. The country today represents some 45 percent of our French African market sales alone with a turnover surpassing 35 million and is the uncontested mega-market in the region: not only in terms of size, but also in terms of strategic relevance as the interface between north and south.”

Oka-Bousbia adds, “It is essential to be physically present to fully understand the local dynamics and engage with right people. Because this is a complicated market it, quite naturally, requires extra attention. For example, Algerian market access issues take up approximately 75 percent of the entire regulatory affairs workload of bioMérieux North Africa, therefore it is logical to want to base the area’s regulatory affairs resources in Algiers rather than in Tunis or Casablanca.”

WHO DARES, WINS

Where does all of this leave international investors vis-à-vis the freshly assertive Algerian marketplace? The growth potential of the market is very high, especially in the pharmaceutical and medical device sectors. “We’re staring at a population that is forecast to reach over 72 million people by 2050 and where the demographics will be structurally skewed towards those population groups that consume a disproportionate amount of medicines,” speculates AHK’s Ackermann.

This means that though the market might be tricky to navigate, it can herald big rewards for those who dare and manage to go about it in the right way. “Make no mistake that Algeria is what we refer to as a VUCA market: one that is characterized by high levels of volatility, uncertainty, complexity and ambigu-



Karim Harchaoui,
country manager,
Novartis Pharma
Services

ity,” stresses Novartis’ Karim Harchaoui, “so to make a success out of it you have to have to have a certain amount of patience and resilience.” A certain amount of courage also appears to be a pre-requisite. “Unless you are willing to take the risks, you may not be rewarded here,” warns Sandoz’s Mourad Ishak.

Rewards can be vast, but they obviously have to be juxtaposed against the risks. “We do not really recommend Algeria to small companies that are starting to export for the very first time. This is the sort of market that is best left to old hands who have sufficient experience. There are many potential pitfalls, but the biggest one is the regulatory uncertainty. The rules of the game are liable to change midway through the game and that means that, as a business, you have to have deep enough pockets and enough time and patience to be able to weather any delays that you might experience,” counsels AHK’s Marko Ackermann. “The bottom line is that this is no place for newbies. This is certainly not the sort of market where you can saunter in, make a fast buck overnight and then withdraw. The businesses that tend to succeed are those that have the perseverance to be here for the long haul and will invest the energy, time and effort in building up trust locally,” he concludes.

The Social Security’s Djaoaud Bourkaib is, however, optimistic that Algeria’s pharma market can continue to grow and gain even more influence within its region. He posits, “We want Algeria to become a regional market. If our neighbors are buying, the Algiers factory will be able to respond to the need. Not only is Algeria a more interesting local market, but it is a potential center of commercial influence. There are challenges to be met, but the authorities have made many decisions to facilitate this.” ❁



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Stunted Innovation in Drug Development?

Data shows cultural gaps and highlights a C-level fix

Most pharma leaders view innovation as vital to improving the drug development process in the US. Yet new data shows the disconnect between the culture of innovation that pharma professionals ascribe to their organizations, and the reality.

To understand perceptions in the industry toward innovation, InCrowd asked 128 pharma executives—representing all major areas from discovery to launch—how they and their respective organizations view innovation.

Part of corporate culture

We found that the majority reported an innovation culture that was strong. Fifty-five percent of respondents report that their internal teams test new technologies that may expedite drug development at least once per quarter. An even larger group—over 70%—agree that their company encourages the exploration and testing of new technologies, often with a sense of urgency.

Despite such encouragement, perceived risks loom. Among total respondents, 30% agreed that exploring new technologies may be too risky or may damage their or their colleagues' careers if implementation failed. Risk concerns were even higher among specific areas.

- Though 90% of respondents who work in commercialization say that their culture encourages them to explore innovations, nearly 40% say those on their team are

afraid that it will hurt their careers if team members try something new and it doesn't go well.

- Figures were similar among regulatory team respondents: 75% said their culture encourages trying innovations, yet 50% were afraid doing so would hurt their careers.
- Thirty-one percent in drug discovery said there are too many risks with new technologies and innovation—even if there are examples that work.

On perceived barriers to innovation, a resounding 80% of respondents mentioned budget, with less than a third reporting sufficient budget to fund the testing of new innovations in their departments. Also cited was internal inertia with processes, management, and culture, as well as accessibility issues.

Ideas for improvements

What's going on here, and what are steps C-level leaders can take to address this innovation gap? Respondents named several areas where friction could be removed from the process, especially innovations in data processing.

- Fifty-three percent listed advanced analytics tools, including bioinformatics and artificial intelligence, as high-impact innovation.
- An additional 19% suggest improved computational modeling for PK/PD and toxicity.
- Others noted advances in assay development (21%), preclinical validation (20%), and drug discovery (16%).

Respondents also cited a number of other technologies that could help them.

- 1. Improved patient recruitment and retention:** Advancement in genomic testing for patient selection, digitization of trials, and mobile monitoring.
- 2. Enhanced system integration:** Oversight of data reporting, information archiving, source data analysis, data verification, and access to tumor biobanks.
- 3. Better analytics capability:** Extrapolation of early phase results to larger populations, quality-of-life surveys, data mining, storage, and retrieval.
- 4. Process enablement:** Library prep, expanding online processes for regulatory submissions, and adaptive clinical trials.

The onus is on C-level management to do what is uniquely in its purview—mitigate the anxiety associated with innovating by finding ways to reward teams for trying new technology regardless of the outcome.

When pharma executives encourage the testing of new approaches that are known to be safe and applicable in R&D—and reward these efforts, even when they learn the innovation was not the best solution—they are furthering the movement to shorten drug delivery cycles.

The impact of even incremental innovation can be profound. Shaving even one week off of the \$2.6 billion, decade-long process to bring a drug to market could save a manufacturer \$500,000. With an earlier launch, companies also lengthen the patent-exclusivity period, garnering them more revenue than planned. Beyond the financial impact is another benefit: more patients receiving their potentially life-changing medicine. **PE**



MEGHAN OATES-ZALESKY is senior vice president of marketing at InCrowd

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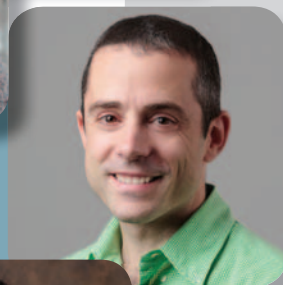
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