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Pharmaceutical Executive

AUGUST 2018
COMMERCIAL INSIGHTS FOR THE C-SUITE
VOLUME 38, NUMBER 8

EMERGING BIOPHARMA

New Frontiers

Hubs Reshaping Innovation in Northeast

Nancy Thornberry, CEO of NYC-based Kallyope, a biotech startup focused on the gut-brain axis.

UBM

URGENT – FY2019 GDUFA Fees Just Announced... Increased by 17%

A New ANDA Holder Program Fee Approach Under GDUFA II

The ANDA Holder Program Fee under GDUFA II is now entering another fiscal year! **A firm and its affiliates pay one program fee each fiscal year commensurate with the number of approved ANDAs** (both active and discontinued ANDAs) that the firm and its affiliates collectively own. The program fee is split into three tiers that represent the number of approved ANDAs held by the firms and their affiliates within the Orange Book.

The ANDA HOLDER Program fee schedule for Fiscal Year 2019 was just published by FDA and fees increased by 17% across the board. Fees due to FDA by October 1 are as follows: small tier (1-5 ANDAs) companies pay $186,217; medium tier (6-19 ANDAs) companies pay $744,867; and large tier (greater than 20 ANDAs) companies pay $1,862,167.

This can represent significant funds for some companies. For those companies with a modest number of ANDAs, they will again be laying out cash for drug products they don't currently market or are identified in the Discontinued Drug Product List section of the Orange Book. **For a small or medium-tier company this can be a dramatic impact in their ability to even retain the assets they worked so hard to obtain**. And YES, **discontinued ANDAs are still considered approved ANDAs for user fee purposes** unless the approval is withdrawn.

In addition, a one-time marketing status report was required to be submitted to the FDA earlier in 2018, identifying the submission as "MARKETING STATUS REPORT / ONE-TIME UPDATE." While there has been **no guidance as to what happens to the ANDAs identified as "not marketed"**, one scenario may be they will be either moved to **discontinued** status or have their approval **withdrawn**.

What is the **penalty** for not paying the program fee? There are three effects if an applicant fails to pay the program fee: (1) If the fee is not paid within 20 calendar days after the due date, the parent company will be placed on a **publicly available arrears list**. (2) Any ANDA submitted by the applicant or its affiliates **will not be received**. (3) All drugs marketed pursuant to any abbreviated new drug application held by such applicant or an affiliate of such applicant shall be **deemed misbranded**.

For the second year a company called **ANDA Repository, LLC**. has successfully offered significant user fee relief and a solution for companies that have discontinued ANDAs or drug products not currently marketed. Imagine, a parking lot. The owner of a car not being used on a daily basis needs a parking space for that car. In exchange for that parking space (and an annual fee) the car's owner transfers title of the car to the parking lot owner. The former owner of the car can, with appropriate notice, take back ownership when he/ she decides they want to use the car again. Since the parking lot owner has enough cars, this has proven to be a beneficial venture for all of the parties involved, and the cars are kept safe and secure.

In the example above, the car owner is an ANDA sponsor, and the parking lot owner is **ANDA Repository, LLC**. In exchange for its services, **ANDA Repository, LLC**. charges an ANDA sponsor an annual fee, which is significantly less than the ANDA Holder Fee the ANDA sponsor would otherwise pay as a small or medium size firm.

There is NO need to pay excessive fees or be forced to withdraw your valued assets due to short-term market conditions, capacity constraints, API supplier issues, etc.!

Alternatively, if your choice is to WITHDRAW the ANDA, we may be interested in purchasing it from you!

The FY2019 GDUFA Generic Drug Applicant Program Fee is due October 1st so please contact us soon!

Phone: +1-570-261-1901 Email: info@andarepository.com

From Science to Success

UPON "FINALLY" COMPLETING MY ARTICLES FOR THIS ISSUE, I happened upon Matthew Herper's recent interview on *Forbes*, http://bit.ly/2mGnE6n. Featured was newly-named chief scientific officer for GSK, Hal Barron, with hiring insights from GSK CEO Emma Walmsley. The article is great, so you must read it, but here are some of Barron's highlights: he worked at Genentech since 1996, has overseen the development of 10 approved drugs, uses a very singular management approach, is focusing on immunotherapy, and believes in genetic data for drug development. Not surprisingly, Barron announced last month a $300 million investment in 23andMe in a four-year collaboration to use the genetic database in drug development.

LISA HENDERSON
Editor-in-Chief
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Will a long-time biotech professional be able to impact GSK's pipeline and make the disciplined decisions that will generate greater sales toward the company's overall bottom line? Most in the article believe he can do just that.

What evolved from our loosely termed "Emerging Biopharma" issue became a look at what turns a biotech into a biopharma, what factors can help transform scientific innovation into commercial success, and what tracks biotech takes in its drug journey. Clearly, Barron's path represents the now-classic example of small biotech growing to the role of larger biopharma.

However, what is a biotech, biopharma, and large pharma have blurred. The former delineation of biotech/big molecule, pharma/small molecule don't hold true anymore, as much of large pharma is on-board with biologics and other cutting-edge therapies. And with more former big pharma professionals bringing their commercial insights and business acumen into biotech, and biotech executives bringing their nimble and focused decision-making to pharma, even organizational descriptions begin to blur.

As we detail in our coverage (starting on page 14), certain geographical regions are betting big to become the next biotech innovation hub a la Boston. We look at Philadelphia, New York City, and New Jersey and Barcelona, Spain, as a vibrant European example. In November, we plan to focus on the Southeast and the West Coast and Midwest early next year.

The editors are also aware of the many other states and regions in the US that are investing heavily in life sciences and innovation. Some clearly have been doing it for quite some time, based on the academic research centers and universities in their area. But there are similarities and characteristics in the areas we initially selected to compare to determine their future potential and ability to rise to the first tier.

Another trend is the location of big pharma innovation centers in Cambridge. Novartis, Bayer, and Sanofi are included in our article, and each has a leader rich with a research background and strategic focus to collaborate with innovators in the region. But as rewarding as science is, it can become less so if the goal of reaching patients with drug solutions is not met.

You will read in these articles a similar thread—science needs to start with the patient and the success of a compound depends on the science, trial design, endpoints, and then clinical and regulatory execution. Commercial success comes after and is closely matched to product differentiation from other drugs on the market.

We've heard the term fail-fast for years, but maybe the term succeed-succinctly would be more empowering

It appears that the emerging biopharma is a biotech that puts equal efforts into the commercial pivot, the step that separates pure science from crass commercialism. A separation of church and state, if you will. As one executive said, "I went to the dark side and came back," but he came back with patient insights from the commercial side to help inform scientists and make those decisions to move forward or not.

I have heard that it can be very difficult for a scientist or medical director to "let go" of a questionable compound, and the reason why some Phase III trials fail is that one person is pushing it against all odds. We've heard the term fail-fast for years, but maybe the term succeed-succinctly would be more empowering.

Pharmaceutical Executive VOLUME 38, NUMBER 8

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Emerging Biopharma: New Frontiers

The Big Apple's Fresh Start in Biotech

Michelle Maskaly, Senior Editor

Though challenges in space and affordability remain, New York City is emerging as a hotspot for biotech incubators, including one unique startup based in the city's fast-growing innovation center, whose CEO, like many C-suite veterans, made the career leap from the big pharma world to forging new discoveries in medical science.

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Cover Photo/Illustration, John Halpern: Nancy Thornberry, CEO of biotech Kallyope, sits in the offices of Alexandria LaunchLabs, a full-service startup platform in the Alexandria Center for Life Science in Manhattan. The photo is enhanced using Photoshop to include the actual NYC skyline from Kallyope's offices.

Innovation, Location, and Inspiration

Lisa Henderson, Editor-in-Chief

Examining the rise and reach of biopharma in the key Northeast Corridor clusters of Boston, Philadelphia, and New Jersey.

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Reigning in Spain

Julian Upton, European and Online Editor

Over the last decade, Spain has seen a significant growth in venture-capital investment in the life sciences. We explore the driving forces.

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The Commercial Pivot

Lisa Henderson, Editor-in-Chief

With increasing responsibilities and decision-making post-discovery, the traditional label of "biotech" is changing.

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Cross-Border Funding Review

By James Leech

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Behind an economic revival in Portugal, including healthcare spending growth, the nation's life sciences sector is benefiting as well, with Portugal diverging from the European averages to show an increase in R&D and innovation.

PHARMACEUTICAL EXECUTIVE VOLUME 38, NUMBER 8 (Print ISSN 0279-6570, Digital ISSN: 2150-735X) is published monthly by UBM LLC 131 W. First St., Duluth, MN 55802-2065. Subscription rates: $70 (1 year), $125 (2 years) in the United States and Possessions; $90 (1 year), $145 (2 years) in Canada and Mexico; $135 (1 year), $249 (2 years) in all other countries. Price includes air-expedited service. Single copies (prepaid only): $7 in the United States, $9 in all other countries. Back issues, if available, are $20 for the United States and Possessions, $25 for all other countries. Include $6.50 per order plus $2 per additional copy for US postage and handling. If shipping outside the United States, include an additional $10 per order plus $3 per additional copy. Periodicals postage paid at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to PHARMACEUTICAL EXECUTIVE, PO Box 6180, Duluth, MN 55806-6180. Canadian G.S.T. Number: r-12421 3133rt001, Publications mail agreements NO. 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, Canada. Printed in the USA.

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Readers Weigh In

It has been shown in a number of cases that pharmacists who advise patients appropriately have a strong, positive impact on adherence. It would behoove the industry to partner with pharmacy to promote adherence and appropriately compensate pharmacists for their effort. As shown in the article, this will have a positive payoff for the companies, for the pharmacists, and the patients they all serve.

Michael A. Schwartz
"Adherence: Addressing Pharma's Last-Mile Problem"
bit.ly/2xPHbK6

I think expecting a response from EMA is to misunderstand the situation. It isn't up to EMA, which must simply follow the rules set for it by EU legislation, just as the industry in the UK will have to follow the rules set for it by the UK government and the UK regulator, whoever that may be. If the UK wants to work with and within EMA after Brexit, it is up to the UK to negotiate that with the 27 [remaining member states] and the Commission.

Anonymous
"EMA Relocation Countdown: Some Industry Viewpoints"
bit.ly/2uQ2nf6

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Specialty Pharma
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Jeffrey Nau, CEO of Oyster Point Pharma, talks about what it's like working on diseases that don't get a lot of press, and offers up best practices in raising startup capital. bit.ly/2uOA6EH

Episode 12: Journey in Regenerative Medicine
Gil Van Bokkelen, CEO and co-founder of Athersys, a regenerative medicine company, discusses the decision to start the firm in Ohio instead of his native Northern California, and shares the secret to staying resilient in the C-suite amid heavy challenges. bit.ly/2NxrACH

Episode 11: Tackling Sports and Science
Former NFL star and current broadcaster, Solomon Wilcots, talks to *Pharm Exec* about the intersection of sports and biopharma, including his work in matching pro athletes who are passionate about a certain disease with biopharma organizations. bit.ly/2yRP6Hv

Episode 10: Mentorship vs. Sponsorship
Michelle and Christen host one of *Pharm Exec*'s Emerging Pharma Leaders, Sabina Ewing, vice president of business technology for Pfizer, who discusses the difference and importance of mentoring and sponsoring in business and pharma. bit.ly/2IAoiLf

Episode 9: Brands of the Year
Michelle and Christen host the *Pharm Exec* editorial team to discuss our selections of Brands of the Year and why we chose to highlight these particular products. bit.ly/2ILwFZe

Congress, Feds, FDA Take Action in Opioid Crisis

Recent bipartisan efforts look to expand access for addiction treatment and stem inappropriate drug prescribing

The House recently enacted multiple legislative proposals to support treatment of opioid abusers and deter inappropriate drug prescribing and illegal distribution. This bipartisan action sets the stage for similar action by the Senate, as the legislators seek to address the deadly drug epidemic before the November midterm elections (see https://bit.ly/2L7Tzuo). A main objective of these policies is to widen access to medications for addiction treatment and overdose emergencies, a strategy backed by pharma manufacturers of buprenorphine and newer rescue drugs and opioid disorder therapies. The legislation also encourages prescribing of non-opioid pain therapies, but stops short of mandating prescriber education on pain management—or of regulating drug prices.

Meanwhile, the Justice Department brought charges against dozens of individuals involved in prescribing and distributing opioids and illegal narcotics as part of a massive healthcare fraud enforcement action across the country (see https://bit.ly/2KV4tjZ). Although most of the 600 defendants face charges related to schemes to bilk Medicare, Medicaid and other government health programs of some $2 billion in fraudulent claims, the campaign also targeted opioid-related activities, with more than 70 doctors and other health professionals facing charges related to "fanning the flames of the opioid crisis."

Shutting down websites

As part of ongoing FDA efforts to reduce illegal opioid prescribing and distribution, the agency seeks to curb the rise in opioid sales through online pharmacies. In June, FDA sent warning letters to operators of 53 websites to halt illegal sales of unapproved, misbranded, and dangerous medicines such as Tramadol and oxycodone, or face product seizures or injunctions (see https://bit.ly/2JsQi81).

FDA also hosted an "opioids summit" to discuss with leading internet operators and other stakeholders ways to reduce the availability of opioids through misleading websites and search engines (see https://bit.ly/2JpROUE). The agency cited a January 2018 report from the Senate Permanent Subcommittee on Investigation indicating that online illicit drug sales reached more than $150 million in 2015, as use of the internet to purchase opioids from online pharmacies has soared (see https://bit.ly/2uOSiSb).

FDA invited leading tech companies to the summit, such as Facebook, Google, Microsoft and Yahoo, as well as online shopping sites, shipping firms, payment processors, and trade associations representing online pharmacies and internet operators. While the tech community maintains that online sales account for only a small portion of illegal drug transactions, FDA Commissioner Scott Gottlieb called for concerted action: "We can't just play whack-a-mole with illegal sites, shutting down URLs only to watch new ones pop up." Cutting off the flow of illicit internet traffic in opioids "is critical," he said, urging attendees to work together to stop the "digital drug dealers."

FDA has increased resources to target and take action against illicit internet drug marketers, despite multiple challenges in doing so. For example, progress in educating health professionals on the importance of reducing prescribing of opioids in favor of less addictive pain medicines now is predicted to send even more individuals suffering from opioid addiction to websites and other sources of illegal and potentially unsafe pills.

Gottlieb acknowledged that the tech firms at the summit have "the expertise to transform this space." He cited efforts by Google to de-index web pages linked to FDA warning letters, by Microsoft's Bing to attach pop-up warnings to such illicit websites, and by Facebook to steer parties seeking opioids online to sites with information on addiction treatment. While there are difficulties associated with implementing these and other strategies, Gottlieb urged further collaboration with the internet experts to devise technological solutions and collective approaches for decreasing opioid availability. PE

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FDA Clears Pathway for Off-Label Economic Communications

After years of debate and discussion, FDA has finalized a more flexible policy for how biopharmaceutical companies may discuss payments, outcomes, and healthcare economic data with payers, formulary committees, and other audiences with expertise in drug prescribing and coverage. By clarifying a safe harbor for such communications, the policy is expected to encourage sponsors to conduct more studies that assess economic benefits of treatments, such as gains in quality-adjusted life years (QALYs) and reduced hospital stays and other procedures.

The broader expectation is that such studies and communications will provide data that support efforts by marketers to propose alternative, value-based contracts and reimbursement strategies, with payments based on expected outcomes and health improvements.

The broader aim is to help "sophisticated parties" with expertise in evaluating such data to assess value-based contracts and innovative reimbursement strategies

The guidance on "Drug and Device Manufacturer Communications with Payers, Formulary Committees, and Similar Entities," announced in June, provides advice to marketers through a question-and-answer format that outlines a broad range of effectiveness, safety, and cost-effectiveness information that marketers may provide to entities involved in formulary management and coverage decisions (see: https://bit.ly/2tcS7iJ). FDA Commissioner Scott Gottlieb acknowledged in announcing the revised document that any information provided to payers must be truthful and non-misleading and be presented in an "open, responsible" manner, with background and contextual information that supports informed decision-making.

FDA further extends the policy to manufacturers of both drugs and medical devices and permits providing information to payers on unapproved products and unapproved uses of cleared products to support coverage decisions related to new therapies and to additional new uses. The broader aim is to help "sophisticated parties" with expertise in evaluating such data to assess value-based contracts and innovative reimbursement strategies. PE

Combating drug shortages urged

FDA needs a more concerted effort to address nationwide shortages of intravenous drugs that put patients at risk and threaten public health, according to a group of leading Senators ranging from Republican Orrin Hatch to Democrat Bernie Sanders. They and their colleagues have expressed dismay about limited supplies of critical, widely used injectable opioids, anesthetics, and sterile IV fluids that continue for months and years. Legislators requested FDA Commissioner Scott Gottlieb convene an authorized Drug Shortage Task Force and develop recommendations by the end of 2019 to ensure that "appropriate supplies of essential medications are always available."

Evidently, these policymakers believe that FDA can do more to prevent shortages than is indicated in the agency's annual report to Congress on drug shortages for 2017, or that Gottlieb spelled out in a statement issued in May (see: https://bit.ly/2J67htx). The annual report indicates that ongoing drug shortages continued to decline from a high in 2012, but that new shortages rose last year, largely due to a devastating hurricane season that ravaged drug production in Puerto Rico, plus the shutdown of a major manufacturer experiencing production difficulties.

Douglas Throckmorton, deputy director of the Center for Drug Evaluation and Research (CDER), responded to the Senate request with specifics on what FDA was doing to address shortages in IV fluids, pain medications, and EpiPen self-injectibles that raise particular concerns from health professionals (see: https://bit.ly/2yw0gkG). Throckmorton provided specifics on how hurricane damage in Puerto Rico shut down Baxter Healthcare production of saline and dextrose-based fluids widely used to deliver medications intravenously.

Tough Fight Looms in Preserving R&D Incentives

European drug innovators ready their defense as the Commission mulls manufacturing waiver for generic competitors

Research-based companies in Europe look as though they have lost one battle on preserving incentives for innovation—but the bigger war is only now really getting underway.

After lengthy reflection, the European Commission decided recently that it is time to ease back on the protection that the supplementary protection certificate (SPC) offers to innovators. It is proposing a Bolar-style waiver for Europe that would allow generic competitors to manufacture stocks even before the SPC expires on an original product they wish to copy.

This so-called manufacturing waiver will simplify life for European copy-product firms by allowing them to start producing a generic or biosimilar for export to non-European Union (EU) markets where this type of protection does not exist. It goes a long way to answering the persistent protests from European generic firms that they lose out in important export markets to manufacturers based outside the EU, and which are not restrained by the EU SPC.

Senior EU officials justified the move as a pragmatic response to an evident challenge. Commission Vice President Jyrki Katainen called it "a well-calibrated adjustment to the current regime to remove a legal barrier that was preventing our companies from competing on equal terms on global markets where competition is fierce." And Elzbieta Bienkowska, the commissioner responsible for industry, predicted a positive impact on growth and up to 25,000 new jobs in the EU, as well as $1 billion net additional sales per year.

But it was greeted with howls of anguish from the European research-based industry, accompanied by warnings that innovative companies might choose to move abroad. It described the plan as an attack on intellectual property rights and a threat to advances in therapy. "It also sends a global signal that Europe is weakening its commitment to IP," the research lobby added, putting at "serious risk" investment, jobs, and European growth.

Since then, however, the group has relaxed a little its view of this element in the IP campaign. A key figure in the research-based sector, Stefan Oschmann, CEO of Merck KGaA, Darmstadt, Germany, admitted in early July that it was time to move on from this particular setback. He is doubtless keeping his power dry for the much bigger conflicts that will be fought over the coming year, and that will raise issues about the substance of the SPC, rather than just a detail about a manufacturing waiver. Related incentives for pharma that offer extended protection in return for research—including the orphan drugs scheme and the pediatric medicines scheme—are also going to become arenas for the fight.

Reaping value?

New heat has been brought to this battlefield by the publication of an EU-commissioned study that aims at assessing the value for money of these incentive schemes. This has provided some support to the research-based industry, but not necessarily enough for it to escape unscathed. Across nearly 400 pages, the study analyses the operation of the five main schemes that were designed to boost EU medicines research, and attempts to reach conclusions as to whether they are really leading to more and better medicines, or merely preventing erosion of drug industry profits by delaying the entry of generic competition.

The good news for the drug industry as it readies itself to defend its incentives is the finding in the study that the average total protection from patents and additional measures declined from 15 years to 13 years between 1996 and 2016—partly owing to increased regulatory requirements, and to the demands of more complex and, consequently, lengthier research and development.

Its case for maintaining these schemes is bolstered by the finding that average development time—from first patent filing to first EU marketing authorization—has increased from 10 years to 15 years. The study says, helpfully, that the accompanying higher risk profile of investments "requires a higher

REFLECTOR is *Pharmaceutical Executive*'s correspondent in Brussels

expected revenue and profit." It is, therefore, not uncommon that there are some "very profitable single medicinal products" to cover the investments that fail to secure a marketed product in the end, the study adds. "A first conclusion is that the incentives and rewards provide the additional protection that they were designed to do," it says.

But in assessing the implications of the additional protection when product availability and accessibility are taken into account, the results are more mixed, and the evidence is "ambiguous." So, the study ducks out of giving any firm advice. "It is not within the scope of this study to advise on the 'right' balance between innovation and lower prices of medicinal products through faster availability of generics; it is ultimately a political decision," it says.

Deciding factors

That "political decision" can come only from the EU's legislative process—and that is in the lap of the gods. The Commission's stated aim is "to provide results by 2019 to allow the next Commission to take informed decision about possible policy options" in the evaluation of the orphan and pediatric regulations. But the ultimate decision will not be in the hands of the Commission, which, in pro-growth mood three years ago, said it was time to "consolidate and modernize intellectual property rights as a way to stimulate innovation and growth within the European Union and to engage in a reflection on ways to improve the patent system in Europe… for pharmaceuticals."

EU law is made by the European Parliament, with its wide assortment of different interests, and by the EU Council, where national ministers meet. And going by many of their recent pronouncements, there is no unqualified admiration for the industry in these institutions.

The parliament's views on incentives can be gauged from its own resolution on access to medicines, which carries, up front, the statement that "the entry of generics onto the market is an important mechanism for increasing competition, reducing prices, and ensuring the sustainability of healthcare systems." It goes on to conclude that "the market entry of generics should not be delayed and competition should not be distorted." In addition, it throws in the observation that "in many cases, the prices of new medicines have increased during the past few decades to the point of being unaffordable to many European citizens and of threatening the sustainability of national health care systems."

Within the Council, the genesis of this review of IP lies in the angry conclusions of health ministers as far back as 2016, when they demanded an inquiry into how these incentive schemes achieved an effective trade-off between innovation, availability, and accessibility of medicines. But suspicion of the drug industry is a constantly-recurring theme. Earlier this year health ministers were invited by the chair of the Health Council to discuss questions such as "How can member states make sure that health comes first before commercial interests?" or "European pharmaceutical industry, committed to health?"

Agendas uncertain

To complicate matters still further, the composition of both the European Commission and the European Parliament will be significantly changed next year, which is when proposals are to be finalized and decisions are to be made. It is impossible at this stage to predict with any accuracy what the character of these institutions will be, but the likelihood is that in the current surge of populism in Europe, many of the successful candidates from the election for the parliament will be from more radical parties rather than the mainstream centrists, and this may well result in more extreme attitudes—including criticisms—of the drug industry and its pricing. Similarly, there is no guarantee that the essentially pro-business agenda of the current European Commission under Jean-Claude Juncker will be maintained under new leadership.

This is a headache that industry leaders are not going to be cured of either easily or rapidly. PE

EU law is made by the European Parliament and the EU Council. And going by many of their recent pronouncements, there is no unqualified admiration for the industry in these institutions

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What's more, if your organization is called into question, do your partners have the regulatory expertise to course-correct compliance issues without interruption to your business? FDA enforcement escalates quickly and requires immediate action. "DLSS was recruited to assist a client that was facing potential FDA action. They did not have the manpower to meet the rigid FDA deadlines, and their vendors required coaching to speak directly with the FDA," says Williams. "You want to make sure your partner has in-house resources to stand by their work."

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"Today, our client's therapy reaches patients within eight hours or less, 24/7, with 100% shipping accuracy. The program has saved 600 lives and counting."

Nancy Thornberry, CEO of biotech company Kallyope, poses in Alexandria LaunchLabs, a startup incubator that, like Kallyope, is housed in the Alexandria Center for Life Science in Manhattan. *(Photo by John Halpern)*

City on Cusp: The Big Apple's Fresh Start in Biotech

Though challenges in space and affordability remain, New York City is emerging as a hot spot for biotech incubators, including one unique startup based in the city's fast-growing innovation center whose CEO, like many C-suite veterans, made the career leap from the pharma world to forging new discoveries in medical science

By Michelle Maskaly

When Nancy Thornberry, CEO of Kallyope, stands in her company's lab inside the Alexandria Center for Life Science, floors above the streets of Manhattan with an expansive view of the New York City skyline, it is one of the last places the industry veteran pictured herself after she left big pharma.

"With the continued growth in biotech, there are an incredible number of opportunities for individuals with deep pharma experience, including operational roles, BoD, and SAB positions, and consulting for both biotech and venture capital firms," says Thornberry, who departed Merck & Co. in July of 2013 after 30 years at the pharmaceutical giant. "I didn't see myself in an operational role when I left Merck, and my goal was to learn more about biotech in general and BoD and advisory opportunities that might play to my strengths." During her career at Merck, Thornberry initiated the program that resulted in the discovery of Januvia and had the rare privilege of remaining involved with the development, commercialization, and life-cycle management of the diabetes drug for the last 10-plus years of her tenure there.

"I joined boards of a couple of private companies I was excited about, and also did some advisory work for some early stage biotechs," she told *Pharm Exec*. "I really enjoyed the work, but periodically missed having more skin in the game."

From time to time, Thornberry "checked out new opportunities," but as she describes it, "nothing really excited me." That is, until she learned about Kallyope, the platform biotech firm.

"Kallyope ticked every box for me," recalls Thornberry. "First, I was seduced by the science and

tremendous potential for the company. The gut-brain axis was an untapped area of biology, and the highly sophisticated platform technologies had the potential to reveal novel biology that could enable the discovery of fundamentally new approaches to diseases of high unmet need. Second, the people involved, including the founders from Columbia University, founding scientists, and investors, were among the best in their respective fields and had a shared vision for the company."

And, last, but definitely not least, location was also a factor in Thornberry's transition.

"The company was to be based at the Alexandria Center in NYC, and I thought it would be advantageous for the company and exciting to be part of the emerging NYC biotech scene," she says.

In November of 2015, Thornberry decided to join Kallyope, just as it was launching.

From the ground up

Starting something from scratch is never easy, but Thornberry used her experience at Merck to help set the foundation for this next chapter of her career, especially her experience with Januvia, which, today, is Merck's second-best-selling medicine.

"This end-to-end experience, and exposure to other discovery and development programs [at Merck] has given me an excellent perspective on the challenges in our business and a good sense of what 'good' looks like to physicians, regulatory agencies, and payers," says Thornberry. "This has been very helpful as we think about new targets in the early space. In addition, the network I developed while at Merck, both internally and externally, has been hugely valuable in tapping into expertise that is needed to advance the company and establish partnerships."

The pharma experience has also aided Thornberry and her team in building a unique culture at Kallyope. "Collaboration is in the DNA of successful pharmaceutical companies, and this same mindset is needed for success in biotech and to build a team that is second to none," she says.

But Thornberry acknowledges there are some things pharma doesn't prepare you for, in her view. "Pharma provides virtually no training in the business side of biotech," she says. "Recognizing what you know and don't know, and asking for help from investors and my broader biotech network, has been critical in helping me advance and finance the company."

Thornberry is a big believer in humility and fully leveraging talent, both internal and external, and working together to advance programs and solve problems. But, with such a high rate of failure in drug development practice, taking science out of the academic world and putting it into biotech with the goal of commercializing it can be extremely difficult.

"I think it's very important for academic entrepreneurs and tech transfer offices to have a good 'gut feeling' for which opportunities truly have translational potential, and also have a realistic view of the value of their discoveries," she says. "It is important for academic centers and emerging companies to bring individuals on board with proven success in pharma and biotech as early as possible to assess the opportunity and get the company off the ground."

Building a community

Thornberry is not just at the forefront of gut-brain health, but she is also part of building an elaborate biotech ecosystem in New York City.

The Alexandria Center for Life Science is a collaborative urban campus developed by Alexandria Real Estate Equities, Inc. One could argue it was this building, strategically placed on the Lower East Side of Manhattan, known as Manhattan's East Side Medical Corridor, that helped put New York City on the biotech map.

Joel S. Marcus, executive chairman and founder, Alexandria Real Estate Equities/Alexandria Venture Investments, co-founded Alexandria Real Estate Equities as a garage startup with $19 million in Series A capi-

"It's very important for academic entrepreneurs and tech transfer offices to have a good 'gut feeling' for which opportunities truly have translational potential, and also have a realistic view of the value of their discoveries."

tal. As it began to build out its offerings to support companies in their development of lifesaving therapies, Marcus's group saw the life science sector's need for strategic risk capital and established Alexandria Venture Investments in 1996.

Marcus views his company, which has buildings like the one in New York City all over the country, as much more than just a real-estate provider.

"We are a key and integrated member of the life science industry," he says. "Our mission to advance human health, overcome global hunger, and improve the quality of people's lives has shaped our differentiated business model, and it is the unifying basis around which we've built our four strategic verticals—real estate, venture investments, thought leadership, and corporate responsibility."

When Alexandria Venture Investments was selected to construct New York City's first life science campus in 2005, it took a big gamble in shifting its focus from acquiring single assets to pursuing an urban cluster campus strategy. When Alexandria Center's East Tower opened in 2010, the investment group was at the very early stages of New York City's biotech scene.

"Creating successful urban innovation clusters takes time," says Marcus. "For example, in the New York City cluster, we are now eight years into what is about a 20-to-25-year process to build a world-class innovation cluster."

Because it sees itself as more than a real estate company and has expanded interests to reflect that, Alexandria Venture Investments is very intuitive about what its tenants will need at different stages, and in a place like New York City where space is at a premium, the company has worked to make it as easy as possible for those organizations within its walls to grow—physically and metaphorically.


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Aerial view of Manhattan's Lower East Side.

"Having the ability to grow our space quickly has been critical, and we are in near continuous dialog with the Alexandria Center to anticipate and enable this expansion," says Thornberry, adding that Kallyope has grown from a startup of six people to a small company of nearly 50 employees. "The Alexandria Center also has an on-site vivarium, which is critical for the research conducted at Kallyope and other biotechs," notes Thornberry.

For a C-suite leader, it's more than just the physical space.

"Being in a place like the Alexandria Center has been particularly important to me as a new CEO, and because we are in NYC, where the biotech scene is just starting to emerge," says Thornberry. "Having access to other CEOs in the center, and meeting others in NYC biotech during their networking events, has been helpful in identifying people, core facilities, potential partners and investors, and other resources that we need to tap into to advance the company."

Developing an ecosystem

It takes more than a single building to develop a sustainable life science innovation hub.

"At a basic level, hubs must combine 'anchor' institutions with capital and managerial talent to create talent mobility," Sarah Kaulfuss, manager, Deloitte Consulting, told *Pharm Exec*. "This is a high-risk industry, especially at the early stages, so hubs need sufficient talent mobility for people to find a new job if their venture fails."

New York City has an advantage when it comes to attracting talent, says Thornberry.

"The founders of Kallyope are from Columbia University, and the desire to have them remain deeply involved with the company was a key consideration in the decision to stay in NYC," she explains. "Proximity to several world-class research and translational institutions was another important factor. Finally, although I'm not sure this was fully appreciated at the time of launch, NYC has a significant edge over other biotech hubs from a recruiting perspective. It is a relatively untapped talent pool and there are outstanding scientists from NYC and beyond who are inter-

ested in living in NYC and working in biotech."

Thornberry notes as well that the city can be attractive to experienced drug discovery scientists from the New Jersey pharma corridor who are interested in making the transition from pharma to biotech. Having incredible science, beautiful spaces, extensive talent, and funding is not always enough, however. A silent but critical driving force to innovation hub success is economic support.

"We have a tremendous ecosystem here, but it didn't happen overnight," said Massachusetts Gov. Charlie Baker during a speech at the June BIO International Convention in Boston. "If you create two great research institutions and wait 200 years, good things happen."

Although his humorous remark resulted in loud eruption of belly laughs from the thousands in attendance, Baker followed it up with a laundry list of public and private investments the government has made over a number of years to make Boston and the state a premier innovation hub for biopharma.

Massachusetts's success was not lost on leaders in New York City, who knew they had a double-edged sword when it came to the life sciences.

"Through in-depth research and interviews with stakeholders, we determined that many young, promising life sciences companies eventually leave the city and move elsewhere primarily because of the difficulties associated with finding affordable, suitable space for long-term expansion," says Shavone Williams, assistant vice president, public affairs for the NYC Economic Development Corporation. "New York has always had an incredible pool of talent in scientific discovery, but one of the biggest challenges we see as a city is developing space for that talent to be able to develop their innovations."

The Alexandria Center for Life Science was one of the first major contributions to helping combat this problem. According to Williams, by the end of 2018, BioLabs, JLABS, and LaunchLabs will all be open, creating a total of 100,000-square-feet of wet lab incubators in the city to help address this spatial issue.

"Hubs need sufficient talent mobility for people to find a new job if their venture fails."

In December 2016, New York City Mayor Bill de Blasio announced a $500 million initiative, LifeSci NYC, with the goal to spur an estimated 16,000 new, good-paying jobs, and establish New York City as a global leader in life science research and innovation. Through a portfolio of 10 initiatives, LifeSci NYC is expected to generate a critical mass of activity by enabling the organic growth of top-tier R&D companies and attracting established R&D organizations that can accelerate a cycle of growth for NYC's life sciences industry.

And with continual funding of the ecosystem, the hope is that it will expand and grow. The city committed $10 million toward developing affordable wet lab incubator space, with the first $5 million grant awarded to BioLabs@NYULangone in 2017. Located in SoHo, it will open its doors later this year. Additionally, JLABS @ NYC, also located in SoHo, opened its facility in June and received $17 million in funding from New York State's Life Sciences Initiative.

"The biotech industry in New York City is constantly evolving," says Williams. "From companies working on innovative medicines like Kallyope, who is working on the gut-brain axis, to Lodo Therapeutics developing drug discoveries through the power of nature, to Epibone growing bones through tissue engineering for skeletal repair. We believe New York City will continue to be on the cutting edge of scientific discoveries in the years to come."

Thornberry shares the same belief. "There is clearly good momentum in building a biotech presence in NYC," she says. "Space has historically been a significant barrier, but the commitment of the state and local governments to this issue is clear, and I'm optimistic that affordable space will be available for new companies going forward. Access to C-suite talent has been highlighted as another issue; however, I believe there is a relatively large pool of biotech CEOs and CSOs who could be recruited to NYC for the right opportunity, and together with the proximity to pharma talent, this challenge can be addressed.

"NYC has a substantial edge over other biotech hubs in recruiting scientists for their new companies. What remains is for the venture investor community to continue to work with local entrepreneurs and academic tech transfer offices to identify exciting translational opportunities to attract key talent and money and fuel continued growth in biotech in NYC." PE

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Innovation, Location, and Inspiration

Examining the rise and reach of biopharma in the Northeast Corridor

By Lisa Henderson

What does biopharmaceutical innovation look like in the Northeast Corridor? For regions such as Boston, New York, Philadelphia, and New Jersey, the unique history, culture, academia, science, and money all play their part in the corridor's biopharma evolution.

During the interviews conducted for this article, it was remarked more than once that "biotechnology" isn't what the company is anymore; it is the business model—what it is before it pivots to commercialization (see article on page 27). While the history of pharma and biotech are separate paths, with the known delineation of small molecule vs. biologic, those lines are quickly blurring in the world of genomics, personalized medicine, and rapidly evolving areas of scientific and medical discoveries, including gene therapy, cell therapy, and gene editing. Many large pharma now have a presence in innovation centers in Boston/Cambridge, along with their historically biologic brethren. Philadelphia, which saw century-old traditional chemical companies such as DuPont evolve into big pharma, which then morphed again through acquisitions and consolidations, is now seeing a rejuvenation from the cell-based research of University of Pennsylvania (UofP) and Children's Hospital of Philadelphia (CHOP) of the past 30 years come to fruition. And New Jersey, with its traditional pharma presence, has seen a revolving door of leavers replaced with comers bringing new biopharmaceutical life back to the state.


Kevin Slatkavitz

Boston

Kevin Slatkavitz, president and founder of Boston-based consulting company ThinkQuality, LLC, and member of MassBio, says of understanding the roots of the current Boston and growing Massachussetts biotech scene: "It has very much been the perfect storm recently in terms of having all the right elements. Typically, you'd follow the science. But research universities like Harvard, the Massachusetts Institute of Technology (MIT), and Tufts have been around forever. So have the major medical centers here. And the emergence and success of local companies like Genzyme, Millennium, and others are not new."

The biotech boom in Boston has, more so, taken shape within the last five to 10 years, according to Slatkavitz. "MassBio has been key, as have investors like Third-Rock, Flagship, Polaris Partners, Atlas Venture, and others," he says. "But I suspect that the other necessary ingredient was then-Gov. Deval Patrick's 10-year, $1 billion investment in Massachusetts life sciences and the creation of the Massachusetts Life Sciences Center, with Gov. Charlie Baker's recent legislation that continues that program another five years and about $500 million. Much like understanding many stories, this one is also about following the money. And all of this infrastructure collectively continues to be an amazing magnet for talent, companies, and serial entrepreneurs; success breeding success."

Lonnie Moulder, CEO of oncology-focused biotech Tesaro, located in the Boston suburb of Waltham, chose Boston to start the company in 2010. Moulder says the decision to locate in the city was easy; he had already been in Lexington, MA, with another company, but says, "We chose Boston for the support and the talent. For our compelling business strategy, we needed access to the talent."


Lonnie Moulder

Similarly, Chris Garabedian, chairman and CEO of Xontogeny, stayed in the Cambridge area when he launched the company in June 2016. Garabedian previously served as president and CEO of Sarepta Therapeutics from 2011 to 2015.

Prior to Sarepta's name change, which Garabedian initiated along with its move to Cambridge, the company was known as Avi, founded in Oregon and located in Bothell, WA. Garabedian needed to choose between Seattle and Cambridge for the new location and vision, and ultimately chose Cambridge/Boston because of the talent. He posted available jobs in both locations but said "nine out of 10 either indicated they would move to Boston or already were in Boston."

Dr. Blaine McKee has been chief business officer for ImmunoGen, also in Waltham, for about two months. Like Garabe-

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dian, he comes to his new company with a wealth of experience specifically in medical devices, along with small and large biotech. McKee also is no stranger to Boston—he received his PhD in Organic Chemistry from MIT, and an MBA in Finance from the MIT Sloan School of Management.


Blaine McKee

McKee said that both the talent and potential opportunities in the Boston area are unparalleled in regard to the proximity to science, as well as the ability to partner with academia, medicine, and industry. However, he did note one challenge. "The job market for sciences is very intense and it's very much in demand," says McKee. "It's quite important that you stand apart from other companies in order to attract and retain talent. It's not always about the money; you can't underestimate culture and the importance of a cutting-edge science."

McKee says that the innovative science or breakthrough science is critical, but in the end, it is more important to bring that science forward to help people. "Financially, sure, it's important, but what really motivates them is the promise," he says.

Besides government support, the venture capital climate in the Boston area cannot be underestimated, as 80% of all life sciences venture capital is currently funneled into the area. McKee noted that the venture capital of the mid-1990's that made San Francisco the leader in biotech has now underscored Boston and Cambridge as the unambiguous leader.

Philadelphia

If you traveled to the J.P. Morgan Healthcare Conference in San Francisco, CPhI in Philadelphia, or to BIO in Boston this year, you would have seen the marketing handiwork of Life Sciences PA in action. The Cellicon Valley campaign—including signs in the airport, billboards, and taxi mentions—builds on a strategic plan started in the early '90s at UofP by then-head of Penn Medicine, Bill Kelley, that ultimately led to it becoming a leader in cell and gene therapy.

Chris Molineaux, president and CEO of Life Sciences PA, says the scientists hired into Penn 30 years ago and fanned out across the region, have turned the area into a veritable family tree of cell and gene therapy. This is evidenced by the FDA approvals in 2017 of Kymriah, the CAR-T therapy begun by Carl June at Penn and completed with Novartis, and Luxturna, a gene therapy for a genetic form of blindness started by Jean Bennett, Al Maguire, and Kathy High at CHOP and developed by Spark Therapeutics. Cellicon Valley built on these successes to influence biotech and life sciences development in the Philadelphia area.


Chris Molineaux

Molineaux says the development work of these academics and industry has attracted contract research organizations (CROs) and contract manufacturing organizations (CMOs) into the area, including Absorption Systems, WuXi App Tec, and others, that has formed an ecosystem that has been quietly growing for the past decade. In addition, he noted there are more than 60 academic institution labs in Philadelphia focused specifically in cell and gene therapies. Moreover, 75% of the vectors being used in cell and immunotherapy research were identified at Penn. Broadly, $450 million is already invested in cell and gene therapy in the area, and each lab employs, on average, 13 researchers and technicians.

If success breeds success, then Spark may win the award for launching biopharma renewal in University City. Steve Rush, vice president of leasing for Brandywine Realty Trust in Philadelphia, said interest from startup biotechs has increased since Spark signed on to be a tenant in Brandywine's Schuylkill Yards, a new 20-year, $3.5 billion mixed-use development on a 14-acre site in the midst of existing buildings and surface lots adjacent to 30th Street Station. That location is home to Amtrak and the regional SEPTA lines, NJ Transit, the subway, trolley, and four bus lines, as well as very close proximity to Drexel University, UofP, and CHOP.

John Furey, chief operating officer of Spark Therapeutics, says the company currently occupies space in three buildings in University City area. It will add additional space in that same area by the end of 2018. He said of the Philadelphia location: "All of the regional features of Boston equally apply here."

Rush echoes similar sentiments. "There is a massive amount of young, talented, educated people in this area that become potential employees for these companies," he says. "What is also of great benefit is the opportunity for corporate partnerships with the universities on

technology, research, and student co-ops or internships.

This fall, Schuylkill Yards will open a public park called Drexel Square, which is located at the center of the development at 30th and Market Streets. The park will be flanked by retail shops and restaurants, and will be the home to hosted events. Besides the attractiveness of the park, Rush explains, "Philadelphia has put in various economic incentives for this location, which is in a Keystone Opportunity Zone, which abates taxes here for 10 years."

The near-west Philadelphia suburbs of Wayne, Pa., is home to Aevi Genomic Medicine, formerly known as Medgenics. Aevi is developing therapies for children and adults with pediatric onset life-altering diseases, including ADHD, Crohn's, and autism. The drug candidates leverage an internal genomics platform and a collaboration with the Center for Applied Genomics (CAG) at CHOP.

Aevi President and CEO Mike Cola previously served as president of specialty pharmaceuticals at Shire, as well as senior positions in product development and commercialization at Astra Merck and AstraZeneca. Cola received his BA from Ursinus College and MS from Drexel. With his background, Cola has a unique understanding of the area's biopharma history.


Mike Cola

"Philadelphia is based in the chemical industry, which is very risk averse, which evolved into the small-molecule pharma companies, which is also conservative," he says. "They were slow to move toward biologics, though they weren't rolling in blockbusters. The revolution of biology—not that chemistry isn't important—and the new era of gene therapy and research into the mechanism of action for underlying disease, traditional pharma didn't have that infrastructure," explains Cola. Prior to regional pharma downsizing, there were about 90,000 pharma employees within a 1.5-hour radius of Philadelphia. he notes, emphasizing that that talent base is largely still here.

Cola believes the city offers fertile ground to grow and nurture young and emerging biotech companies. "There is certainly room to bolster the growth of our industry in Philadelphia, primarily through increased alignment between several key players—the local and federal government and investors, to name a few. We have all the right ingredients in place within our city limits."

New Jersey

It's difficult to have a conversation that includes New York City and Philadelphia without discussing New Jersey—something that people as far back as Benjamin Franklin have observed, when he allegedly said that New Jersey was the barrel between the two cities. Also, we couldn't pinpoint one specific city to single out the most in New Jersey because the state itself is seeing life sciences renewal in multiple regions. But no matter where that renewal is occurring, Debbie Hart, founding president and CEO of BioNJ, says, "The growth of New Jersey's biopharmaceutical industry—including additional jobs, establishments, venture funding, and collaboration opportunities—is a testament to the strength of the state's innovation ecosystem. Our companies and research universities continue to deliver unprecedented medical innovation to patients around the globe, with nearly 50% of all new 2017 drug approvals coming from companies with a footprint in New Jersey."


Debbie Hart

For example, Fort Lee, NJ, is the recently announced new location for Korea-based Enzychem Lifesciences, a global biopharma company founded in 1999. In a recent *Pharm Exec* article (view: https://bit.ly/2Lk426U), Ki-Young Sohn, chairman and CEO of Enzychem, cited the reasons for choosing Fort Lee: "There are many big pharma and biopharma companies headquartered in the New York and New Jersey area. Plus, the proximity to New York, which is the center of finance."

Hart says the 2012 exit of Roche from Clifton and Nutley, which marked the end of the three-year transition of the Genentech-Roche merger, was a huge blow to the Garden State. In 2009, 1,500 jobs were lost or moved to South San Francisco, and another 1,000 when the company made the decision to close and raze its 116-acre campus. Ultimately, it saved five buildings on the campus, one of which was renovated to become—six years later—the Hackensack Meridian School of Medicine at Seton Hall University. It opened to its first class of 55 students on July 9.

The former Roche campus development, called ON3, is similar in vision to Schuylkill Yards. It will feature a mix of offices, R&D, residential, and retail, along with potential lodging and entertainment concepts.

Keys to Success

» Research/ hospitals/health systems

» Discovery/ academia/ universities (tech transfer)

» Students/ scientists

» Number of biotechs

» Transportation

» Economic investment from state or local government

» Key FDA approvals/pivot for commercialization

A 35-mile drive south of the new medical school is Celgene, which earlier this year opened its Thomas O. Daniel Research Incubator and Collaboration Center on its campus in Summit.

Forty miles south of Celgene is the intended redevelopment site of "The Hub," in downtown New Brunswick, a recent project announced by NJ Gov. Phil Murphy and Rutgers University. The site, approved for up to four million square feet of commercial development, is adjacent to the New Brunswick train station, and close to existing corporate, medical, and academic research activity and public transportation. In a recent *New Jersey Business* article (view: https://bit.ly/2LIyrb8), Alex Gorsky, chairman and CEO of Johnson & Johnson, said it is "a natural location for this innovation hub" because, again, it is near "the world's financial capital," top companies, research universities, and leading medical centers. The development plan is just starting, so no timelines are yet available.

Another 30 miles southwest from the New Brunswick location is the recently opened Princeton Innovation Center BioLabs, formed by Princeton University and BioLabs, a professional lab management company based in Cambridge. Though not just for biomedical research, the 31,000-square-foot hub includes fully equipped work spaces for biology, chemistry, and engineering companies, with 68 lab benches, private offices, and shared desks for more than 200 scientists and entrepreneurs. When full, the hub will house 25 or more small companies, most with only a handful of employees.

According to Hart, Princeton BioLabs and the Rutgers involvement in the New Brunswick initiative are just a few examples of recent activity by NJ-based universities, which have reexamined their internal tolerance for technology transfer, no longer insulating themselves but opening up to the possibilities for research collaboration. The state recently launched Research with NJ, a database aimed at boosting collaborations and relationships in STEM fields at five universities, including New Jersey Institute of Technology, Princeton, Rowan University, Rutgers, and Stevens Institute of Technology.

Is there a secret sauce?

"What has happened in Cambridge is truly extraordinary," says Hart. "But there is room for a lot of different models and different players." Based on what *Pharm Exec* editors learned interviewing and researching the articles for this section, we developed our own list of key success factors for regionally-oriented biopharma innovation hubs (see sidebar).

Number one, not on our list, is affordability. For the Cambridge/Boston area, the growing presence of big pharma has resulted in increased rental rates for office and lab space. "But that's balanced with the sheer opportunity to get different experiences," says Moulder. "Many small biotech depend on pharma for collaborations and deals."

Cola says the cost of starting up a company in Boston or New York City is expensive. And then where does the workforce live? In both cities, access to the less expensive suburbs via public transportation is key. But a number of experts also mentioned living in the Philadelphia area, and commuting to Boston via Amtrak or plane. "There is a lot of convenience in Philadelphia," says Cola. "The cost of the market is less, it's between NYC for the financial piece, and DC for the access to the FDA."

Hence, we tabled rents and affordability from our list in lieu of the proximity to good transportation options as a factor for success. PE

LISA HENDERSON is *Pharm Exec*'s Editor-in-Chief. She can be reached at lisa.henderson@ubm.com

Innovation Hubs: At a Glance

NEW JERSEY

Life sciences establishments

» 3,280 life sciences entities

» Approximately 1,000 pharma and biotech companies

Academic institutions

» 63 academic institutions

» 20,000 life sciences graduates each year

Incubators

» New Jersey has four biopharma incubators

» Plans for three more in the near future

Economic impact

» The estimated annual economic impact of the life sciences industry in NJ is $47.5 billion

Funding

» NJ institutions received $240 million in NIH funding in 2016

» From 2014-2016, 19 NJ deals received venture capital funding investments, totaling $255 million

» Between 2010 and 2015, NJ received 186 Small Business Innovation Research (SBIR) awards, totaling $89 million

Employment

» Over 120,000 life sciences workers (of which 65,000 are biopharma)

Transportation

» Local: NJ Transit trains and buses

» Airports: Newark Liberty International Airport, Atlantic City International Airport, Trenton-Mercer Airport

» Trains: Amtrak, NJ Transit

» Buses: Public and private transit

(Sources: https://bionj.org/wp-content/uploads/2018/02/BioNJ-Stat-Sheet.pdf; https://bionj.org/wp-content/uploads/2018/02/BioNJ-Full-White-Paper-012918.pdf; http://assets.njspotlight.com/assets/17/0718/1940)

BOSTON/CAMBRIDGE

Life sciences establishments

» 250+ biotech companies in Boston-Cambridge

» 225+ biotech companies in the areas right outside of Boston (Worcester/ 1-495; Northeast, 128/Suburbs)

Biotech Investment: Reigning in Spain

Over the last decade, Spain has seen a significant growth in venture-capital investment in the life sciences. We look at the effect on the country's evolving biotech sector

By Julian Upton

In March 2017, Labiotech.eu reporter Clara Rodríguez Fernández wrote that she noticed there was "far less biotech news" coming from her home country, Spain, than from the UK, France, or Germany. She tapped three of the country's biotech leaders for a check-up on the sector's health, and was heartened that they all agreed that "the country is at an inflection point for growth and international recognition." Concluding that Spain is overcoming the challenges of the past and starting to catch up with other European countries, Rodríguez Fernández said it was "clear that we'll start hearing more and more about Spain's biotech in coming years."

The Labiotech report eschewed some of the issues that still restrict the country's biotech sector from stealing a march on some of its European neighbors, and it did not dwell on the conspicuousness of Barcelona's towering lead over the other Spanish biotech hubs. But it shone a light on how, following its difficult journey through the global financial crisis, Spain has emerged as a region that has been quietly pressing ahead with a privately-financed agenda of investment in innovation, with a growing number of success stories under its belt.

Following this lead, *Pharm Exec* caught up with some of the key players in Spain's evolving biotech ecosystem to explore their contributions and opinions, and to gauge how much this new sense of optimism is warranted.

Influx of capital

The big catalyst for the increasing vitality of Spain's biotech sector, particularly in the Catalonia region, has been an influx of venture capital. Catalonia now has 29 local investment bodies investing in life sciences; the five key firms specializing in the sector are Caixa Capital Risc, Inveready, Healthequity, Alta Life Sciences, and, particularly, Ysios Capital, the biggest biotech VC in Spain. Ysios's co-founder and managing partner, Joël Jean-Mairet, told *Pharm Exec*: "Great science has been here for decades; we have top hospitals, centers of excellence, and high-quality research. But it's only now that this research is being translated to industry, and venture capital is behind this."

Founded in 2008, Ysios Capital's rise was helped by some fortuitous timing—the company closed its first fund three weeks before the collapse of Lehman Brothers. "If we had aimed to close just a couple of weeks later, it would have been a different story," says Jean-Mairet. However, the biotech sector has been relatively immune to the financial crisis in Spain "because equity VC financing allows biotech companies developing products to finance themselves. Other financing options, such as debt financing, are not possible because such companies obviously do not have any cash flows," Jean-Mairet explains. Moreover, M&A activity between large pharmas and biotech companies has been relatively stable "because large pharmas are con-

Academic institutions

» 48 colleges

Incubators and Accelerators

» 28+

Economic impact

» $13.4 billion in wages in 2016

Employment

» 66,414 employees

Funding

» Massachusetts received $2.6 billion in NIH funding per capita in 2016

» Venture investment in MA biopharma was $2.9 billion in 2016. Other MA life sciences companies raised $430 million in venture capital in 2016

» Cambridge based companies received 59% of all biotech venture investment in the state

Transportation

» Local: MBTA Bus, MBTA rail subway (nicknamed "T")

» Airport: Logan International Airport

» Trains: Amtrak: Acela Express, Northeast Regional (Northeast Corridor to and from NYC and Washington, D.C.), Lake Shore Limited (to and from Chicago), Downeaster (to and from Portland, Maine)

» Buses: Greyhound, Megabus

» Waterway: Port of Boston, passenger boat services

(Sources: http://files.massbio.org/file/MassBio-Industry-Snapshot-2017.pdf; https://masstech.org/why-massachusetts/other-technology-resources/incubators-and-accelerators; http://www.masslife-sciences.com/wp-content/uploads MLSC2018-Impact-Report.pdf)

GREATER PHILADELPHIA

Life sciences establishments

» 1,659 entities

» 4 NCI-designed cancer centers

» 10 medical centers

Academic institutions

» 90+ colleges and universities

» 13 university-industry partnerships focused on life sciences

» 6 medical schools

» 400,000 students

Economic impact

» The industry generated a total (direct and indirect) state economic output of

cont'd, next page

stantly seeking disruptive product candidates and are cash rich."

Over the past 10 years, from investment funds totaling close to €200 million, Ysios has invested in some of the major biotechs in Spain, including Sanifit, Minoryx Therapeutics, Aelix, STAT-Diagnostica (STAT-Dx), and Cellerix, which reverse-merged with the Belgian company TiGenix. STAT-Dx, which develops multiplex diagnostics for molecular analysis of common syndromes, was financed by Ysios and other international VCs, with over €40 million, and sold to QIAGEN earlier this year for $191 million. ("From scratch to exit was just six years," says Jean-Mairet.) TiGenix, which exploits the anti-inflammatory properties of stem cells to develop novel therapies for serious medical conditions, was acquired by Takeda this year for €520 million.

The importance of the specialized VCs for the Spanish life sciences sector cannot be underestimated. Before the arrival of firms such as Ysios, as Sanifit's Joan Perelló explains, talking to general investors was like "speaking another language." He says: "They talked about sales, revenues, short-term ROIs, breakevens, etc. I'm not saying those are not important concepts, but biotech stories are different stories. They are about building value, investing huge amounts in R&D. It was really challenging to raise money outside Spain until Ysios made its move. Now we can talk about these things with specialized investors."

Prior to Ysios, Jean-Mairet was all too aware of dealing with venture investors when he was "on the other side of the table" in his role as founder of a biotech developing a leukemia treatment (a company he later sold to Hoffman-La Roche). "I didn't like it when a VC took three months to reply to my emails," says Jean-Mairet. The experience urged him to push Ysios to speed up its own process when he saw it was starting to take more time to get back to proposals. "I said 'We can't have this', so we instigated a process whereby every week we screen for things that we should look at. We may end up telling a company 'Thanks, but no thanks,' but we communicate that to the company very rapidly; we don't take three months."

VCs such as Ysios have given Spanish companies "more visibility to the outside world," says Jean-Mairet. "There have been sizeable international rounds in the last couple of years; quite a few corporate venture funds—Novartis, Roche, and Lundbeck, among others—have invested in Spanish companies. This was in part thanks to Ysios Capital, because if you don't have a local lead, raising money in other geographies is more difficult for biotech companies."

Perelló notes that after Ysios decided to lead its last financing round, Sanifit was able to attract "a very powerful syndicate of international investors, including Baxter Ventures and the Lundbeckfonden." As Perelló told Labiotech.eu (March 14, 2017), "If you are a biotech in Spain looking for international investors, everyone wants to know Ysios's opinion."


Joan Perelló

Homage to Catalonia

As mentioned, Ysios and Spain's other key specialist VC companies are all based in Barcelona. The Catalonia region also is home to some of Spain's biggest pharma companies, including Almirall, Ferrer, Grífols, Bioibèrica, Reig Jofré and Uriach, and is the Spanish base for multinationals like Amgen, Novartis, Sanofi, Roche, Bayer, Boehringer Ingelheim, and Lundbeck. Among the biotech success stories from the region are Orzon


Joël Jean-Mairet

(cont'd from previous page)

$88.5 billion, comprised of a direct economic impact of $48.8 billion and an indirect of $39.6 billion in PA

Employment

» 53,594 employees

Funding

» $913.5 million in NIH funding

» $389.3 million in VC

Transportation

» Local: SEPTA buses, rapid transit, commuter rail, trolleys

» Philadelphia International Airport

» Trains: Amtrak (11 intercity routes), SEPTA Regional Rail (access to 13 routes from main rail station)

(Sources: Pennsylvania Life Sciences Industry report; Greater Philadelphia Region Life Sciences Report; An evolving industry: Today's clusters creating tomorrow's breakthroughs; all supplied by PhillyBio)

NEW YORK CITY

Life sciences establishments

» 3,514 companies

Employment

» 78,872 employees in 2016

Funding

» $2.4 billion in FY 2017—in VC investments and in patent activities

Transportation

» Local: Subway, taxi cabs, MTA buses

» Airports: LaGuardia Airport, JFK , Newark Liberty International Airport

» Trains: Pennsylvania Station, Grand Central Terminal, Amtrak, Metro-North Railroad, NJ Transit, Staten Island Railway, Long Island Rail Road, Port Authority Trans-Hudson (PATH)

» Buses: Port Authority, mix of public and private buses

Genomics, Aelix Therapeutics, AB Biotics, and the aforementioned STAT-Dx.

According to Biocat—whose mission is to promote innovation in the Calatan system by collaborating with university/research institute technology transfer officers and connecting the best projects with investors and pharma companies—the Catalonia BioRegion hosts 259 biotechnology companies. In Europe, Catalonia ranks third for biotech companies per capita (just behind Sweden and Switzerland); since 2010, on average, one new company per week is set up in the region. Between 2015 and 2017, biotech companies in Catalonia attracted more than €165 million ($193 million) in investment, 55% higher than 2013–2015. What's more, Catalonia boasts 41 research centers and 780 research groups in healthcare and life sciences; 18 university hospitals; three large science facilities (ALBA Synchrotron, the Barcelona Supercomputing Center, and the Centro Nacional de Análisis Genómico); seven technology centers; and 14 science and technology parks with activity in life sciences. Across all sectors, 21% of Spain's researchers work in Catalonia.

This begs the question: when we talk about Spanish biotech, are we talking mainly about Catalonia and Barcelona specifically?


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Sagrada familia skyline at dusk in Barcelona.

Catalonia's pharma and biotech space has a developed entrepreneurial culture, says Jean-Mairet. Barcelona's hospitals, business schools, centers of excellence, and research tradition have seen the industry flourish there more than the rest of Spain. For Biocat Strategy Director Jordi Naval, in addition to the significant economic growth in recent years, the presence in Barcelona of major companies like Almirall and Grífols "have created a source of talent and professionals, who know the pharma business, and a whole ecosystem of providers, from quality assurance to chemistry, manufacturing, and control (CMC) to regulatory affairs. This talent pool has been vital to the region's development."

Naval reiterates that "there is a healthy entrepreneurial spirit. People make the jump from academia and set up companies. You can also see this in the region's other sectors, such as digital and e-commerce." He adds: "We have been living in a startup ecosystem, but now the ecosystem is scaling up, which brings in more investment and more talent."

Perelló, however, is keen to widen the focus outside Barcelona and Catalonia. "If we look at what happened 20 years ago in the US, I think it's the same here. People tended to concentrate in specific areas—Boston, San Francisco, San Diego, Chicago—because it was more efficient for investors, for companies, and for tech transfers," he says. "In Spain, you have Barcelona, for sure, but you also have Madrid and the Basque Country. Sanifit is based on the Balearic Islands (Mallorca), which

» Ferries: Staten Island Ferry, New York Water Taxi, ferries from NJ to Manhattan

(Source: https://www.bio.org/sites/default/files/NY-BIO2018%20-%20state%20profile.pdf)

BARCELONA, CATALONIA

Life sciences establishments

» 1,100 startups

» 14 science and technology parks

» 104 hospitals

Academic institutions

» 780 research groups working in 41 research institutes

» 12 universities offering biosciences degrees

Employment

» One in five researchers in Spain work in Catalonia. More than 5,600 researchers work in Catalan hospitals and research centers

» 10,000+ employees from startups

Funding

» More than €$100 million in 2017. In 10 years, the number of international investors participating in life sciences companies based in the BioRegion of Catalonia has grown from zero to 43, almost doubling in the last two years

Transportation

» Local: Barcelona Metro, Rodalies Barcelona (commuter rail)

» Airport: Barcelona Airport

» Trains: Media distancia Renfe (regional rail)

» Trams: Trambaix, Trambesos, and Tramvia Blau

» Buses in Barcelona

(Sources: Highlights of Barcelona and theBioRegion of Catelonia; Study on investment in the biomedical industry in Catalonia 2018; Achievements and future challenges)

— Christen Harm

is a rare situation, but in 2015 we closed the largest private financing round ever in the Spanish biotech sector (€36.6 million)."

Perelló started Sanifit in 2004 with the vision of becoming the leading company in the field of calcification diseases. "We now have a Phase III-ready clinical asset, which we hope will be our first marketed drug," he told *Pharm Exec*, "and we are pushing to diversify the pipeline to attack other disorders." Sanifit is now "keeping a close eye on potential IPO opportunities in the mid-term," says Perelló.

Nathan Waller, managing director, EMEA, of health technology company Medrio, points to firms in Madrid that are breaking through with pioneering treatments. Cellerix, now TiGenix, which uses stem cell technology to treat perianal fistula, regenerating the skin and closing the wound, is one of Madrid's success stories. Medical device company Medlumics, developing a first-in-class, optically guided heart catheter with a built-in suturing device, is another. Madrid is also home to Spain's largest public biotech, PharmaMar, founded in 1986. Back then, according to the company's oncology business unit head, Luis Mora, the Spanish biotech sector "was not known by the public or even by the authorities" (Labiotech.eu, March 14, 2017). PharmaMar, which "takes inspiration from the sea to discover molecules with antitumor activity," was the first company in Spain to launch a Phase I trial (in 2001). Today, it has a market cap of over $400 million.

Spain as a whole, says Perelló, offers "good science, good projects, and the profile of the entrepreneurs is very special. It is very cost efficient and has been able to raise public funds from competitive European and international projects, which means added value for investors." He also points to the country's high concentration of projects, international airports, and good climate as other advantages. "It is an attractive hub for everyone," says Perelló. For Waller, who moved to Spain from the UK in 2006, the country "is a great place to live and do business. There's something in the Spanish psyche about fighting through adversity, and this spills over into business."

Most biotech activity, however, remains focused in Barcelona, which Naval sees as continuing to grow much faster than Spain's other regions. "We are already on the path to where investing in Barcelona is as easy and straightforward as investing in Amsterdam, Brussels, or Berlin," he says. "Once you start bringing in J&J or Roche, for example, they see that all the elements are in place here: the lawyers, the experts, the clinical expertise." Naval adds that the region's main hospitals are very collaborative in conducting clinical trials and the recruitment capacity in the main indications is high. "If you have the company, the investors, and the CMC all in the same place, and are able to conduct the clinical trials in the same region, it makes life much easier from a startup or biotech point of view," he says.

And with its dynamic cultural offerings, climate, and quality of life, Barcelona is an attractive destination for C-suite talent from the US, the UK, and the rest of Europe. "We have the advantage that talented and innovative people really want to move here," says Naval.

Maintaining momentum

There is, of course, plenty of room for development in Spain. As Perelló points out, R&D expenditure at the country level is 1% of GDP. "It is difficult to reach critical mass with those levels of investment," he says. "Projects come from universities, from hospitals, from tech transfers, and you have to feed all these institutions, not to create more quality but a higher quantity of quality. We have some success stories now, but we need more." It has been difficult, Perelló adds, for researchers from universities, hospitals, and research centers to create their own companies. However, there have been recent improvements in the system with regard to tech transfers to private companies. Pointing to the Spanish BioIndustry Association's (ASEBIO) road map for the education and training of professionals in the new employment niches created by the bioeconomy, Perelló says, "While the situation is still not optimal, we now have a framework."


Jordi Naval

Naval agrees that, even in the Barcelona region, "there still is an opportunity gap between the scientific potential and the number of startups that have begun operations." But, he emphasizes, "smart investors are seizing the opportunity and it is gaining momentum."

For his part, Jean-Mairet predicts more consolidation over the next two to three years. "I think we will see more transactions, more international rounds, and hopefully more exits," he says. "The ingredients are there now for Spain's biotech activities to have more international appeal for investors. We have the talent, the science, the infrastructure, and we have the capital." PE

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Face It. You're Not a Biotech Anymore

The growing need for a commercial mindset in scientific discovery

By Lisa Henderson

Call it the commercialization pivot. There comes a time when a biotech—which has 90% of its financial value in one candidate, has been vested in one indication, knows the science of that compound inside and out, and is singularly focused on that scientific execution—has to take the next steps and execute on clinical development, regulatory, and then, potentially, commercialization.

Chris Garabedian, chairman and CEO of Xontogeny, noted one of the key pieces missing for much of biotech is access to the right people to make drug development decisions. And that's not just a plug for Xontogeny, which offers exactly those services. Ninety percent of all biotechs fail, but Garabedian doesn't believe that they all fail because of technology risks; they fail because of the design, chosen endpoints, or short cuts in science. "There are three key challenges that have emerged in biotech," he says. "There is a lack of sufficient drug development talent across biotech; there is a huge pile of intellectual property that needs to be developed and incubators create more and more IP, but there is no increase in turning that IP into a company."

When Aevi Genomic Medicine's President and CEO Mike Cola refers to the large number of talent still located in the PA-NJ area, he is specifically talking about those professionals with the knowledge of regulatory affairs, clinical development, GCP, market access, sales, and commercialization. Those same skills that Garabedian says are elusive in second- or third-tier innovation hubs, and, overall, small biotech are rife in PA and NJ. Besides the access to talent and other factors, FDA approval is the final key factor for regional innovation hub success. Garabedian noted that what separates the second-tier markets from the top ones is the commercial breakout. "You need a commercial success to form the backbone of the innovative hub," he say. For Boston, the successes were Genzyme and Millennium. For Philadelphia, Spark Therapeutics can take home the trophy for a recent FDA win. For NYC, Synergy Pharmaceuticals recently gained an indication expansion approval for its drug Trulance.

Discovery access

To ensure their access to and ability to foster success in promising therapies is the reason behind many large pharma establishing innovation or incubation centers globally and in the US.

The first to land in the Boston/Cambridge area was Novartis, which established its Novartis Institutes for Biomedical Research (NIBR or "nibber") there in the early 2000s. Dr. Stephen Moran, global head of strategy for Novartis, says, "It was a bold move to take R&D out of Switzerland. Cambridge wasn't the big hub it is today, but [former CEO Daniel] Vasella had a vision and a philosophy." Moran says NIBR's fit in the current Novartis strategy is multi-faceted. With the explosion of scientific developments, such as gene therapy and CRISPR; platform technology for cell therapy and T-protein presentation, and additional therapeutic areas, companies need diversity of science. "There is a fragmentation of sources of innovation…75% of new molecular entities approved by the FDA originated outside of the top 30 pharma companies last year." Moran elaborates that big pharma largely missed the early days of biologics, "and we aren't going to miss that again."

He says that NIBR scientists are "pure of heart and mission," and are directly tied to Phase I, II, and III clinical trials—or as Moran calls it, "the reality of medicine." He says it's still hard to make decisions, because scientific discovery isn't linear. "Finding the balance between scientific and market decisions is a constant struggle of knowing what to prioritize and stop," says Moran. Commercially, he explained, maybe the thought is to discontinue a program, but then a breakthrough is made. Or the breakthrough leads to a very small market for the drug, so then decisions around getting into a larger market come into play.

Stephen Moran

As Dr. Chandra Ramanathan, vice president and head of the East Coast Innovation Center at Bayer and member of the *Pharm Exec* Editorial Advisory Board, noted: "Innovation becomes meaningless if you can't translate it to patient needs."

At the Bayer innovation center, Ramanathan says they have a laser focus on identifying and cultivating partners that can address patient needs. From discovery, to development, to commercial, as long as the patient is at the center of the decisions, success will al-

ways come back to the patient, he believes. "In evaluating new collaboration opportunities, you have to ask, could the biology potentially translate into addressing unmet patient needs? If companies haven't thought about that question, then they really need to rethink their strategy," says Ramanathan.

The Bayer executive started his career as a genomic scientist doing research, then moved over to the commercial side, and is now leveraging the best of both experiences to guide companies to bring the next innovations to fruition. He says, "I love it. I went to the dark side and came back with better appreciation of customer insights. I help start-ups apply those insights—how to best leverage the biology to deliver the most value to the patients."

"Finding the balance between scientific and market decisions is a constant struggle of knowing what to prioritize and stop."

Moran and Ramanathan note that being a part of a large pharma in a biotech-centered location can be challenging. "We want to be the partner of choice," says Moran. To that end, Novartis has many collaborations, including academic-based with the University of Penn and Harvard, and digital collaborations with Pear Therapeutics and Google. Recently, NIBR has added its own partnering organization to extend the reach of those collaborations and facilitate growth. A sign of the times, as Moran explains, "Previously, we were a bit guarded. But we realized we need to open that up and make it a more formal part of our strategy." Moran notes these partnerships and collaborations enable Novartis to scale on three fronts—knowledge, platforms, and capabilities—to network across the ecosystem.

That Cambridge ecosystem, says Gary Nabel, chief scientific officer and head of the North America R&D hub for Sanofi, is one that people could take for granted. Nabel, whose college, medical school, and post-doctoral work were all conducted in Cambridge, says, "It's like a garden. You have trees, flowers, bushes, animals, water, sun. But take one thing away, say bees, and the whole thing would collapse. With Cambridge, you don't have to worry about sustaining the ecosystem."

Like Novartis and Bayer, Sanofi had begun to launch global innovation hubs in the mid-2000s, but Nabel says the Genzyme acquisition really established the company as a leader and it is the number one life sciences employer in Massachusetts. Nabel, though, is very proud of the science that has come out of the Sanofi/Genzyme breakthrough labs. "I'm proud of our company partnering and looking for external partners. We get behind innovative approaches and take them across the finish line."

The pivot

In a recent webcast sponsored by IQVIA (register for free on-demand, http://bit.ly/2zBl9LV) titled "A Framework for Successful Biopharma Launches," experts delved into the launch profiles and insights for emerging biopharma. For example, IQVIA data of 605 launches from 2007–2016 shows 40% were from top 25 pharma, 30% from medium, and 30% from emerging biopharma companies based on those who commercialized the product, not developed it. However, optimizing first-year sales presents challenges. Average first-year sales growth for large pharma was $114 million, $42 million for medium, and $28 million for emerging. This compares to the first-year promotional spend of $53 million, $36 million, and $17 million, respectively.

Further IQVIA data showed that emerging biopharma that partnered for larger investment appears to have little advantage from a revenue perspective. However, because of large pharma's experience with access and payers, partnering does appear to positively affect market acceptance. When partnering with large pharma, prescription fill rates for the emerging biopharma increased 8% vs. going it alone. Promotional spend for emerging biopharma partnering vs. going it alone features a $32 million gap.

Out of 181 emerging biopharma launches examined by IQVIA, 8% were characterized by a high market need with a high product differentiation. Of those, 79% chose a go-it-alone strategy. IQVIA experts theorized that those companies knew the value and science of their drug, thus their decision.

While all product launches have challenges, IQVIA noted that the quality of pre-launch preparation—resources, alignment and processes—is a key factor for post-launch success. Therefore, they stress for the emerging biopharma, the need to hire the right people (or lean on vendor partners), have cross-functional visibility, and management and start preparation early.

John Furey, chief operating officer of Spark Therapeutics, and

Pharm Exec Editorial Advisory Board member, joined the company from Baxalta (now part of Shire), prior to the approval of the gene therapy Luxterna, specifically to ready Spark for that pivotal step. He says, "The benefit of emerging biotech companies like Spark Therapeutics is that you can be nimble and act quickly as a cross-functional team to have a big impact. We leveraged every minute pre-launch to prepare for a historic and unique launch—the FDA approval and launch of the first gene therapy for a genetic disease in the US."

Furey adds, "What are the core competencies of large pharma? Clinical design, regulatory, and commercialization." Spark has a go-it-alone strategy for the US but has entered into a licensing agreement with Novartis to leverage its regulatory and commercial expertise non-US, when and if Luxterna is approved globally.

Nabel says, "The market forces in industry are ruthless. You have to pay attention to scientific rigor and market discipline. It forces you to create value for all the stakeholders. It has to be meaningful for patients and regulators, the costs to manufacture, as well as the payers."

That complexity clearly drives some of the decisions around going it alone in commercial or partnering. Biotech, itself, has many exit strategies, of which FDA approval is but one, says Nabel. "The biotech model vs. the pharma model is that biotech has exits at any given stage to increase the overall value of the company, without ever having sold a product, " he says. "Now, pharmaceuticals companies get very little credit and are only rewarded when a product gets into the market.

"I think it's great that pharma—of all people—are taking up all the leads from academia and biotech and pulling it altogether for success."

'Emerging' Product Launch Strategies

It's tempting for commercial leaders at emerging biopharma companies to simply replicate the approach adopted by their big pharma counterparts when launching products. However, established and emerging companies face vastly different situations at launch. For one, specialty and startup biopharmas have the opportunity to build their commercial strategies from scratch. Second, they often must launch with fewer resources than larger companies.

As they formulate and lay out their launch roadmap, emerging biopharma commercial leaders should consider several key strategies.

Prioritize data. Without robust and organized data, it's difficult for a product launch to get off the ground. With the right customer and market data on hand, a company can create a comprehensive data infrastructure from which it can pull valuable insights that help it make accurate sales projections, design sales territories effectively, and thoughtfully segment the target universe. But collecting, organizing, and analyzing data requires thorough planning.

An emerging pharma company should start by collecting data selectively. It may be tempting to purchase every available type of data—claims, procedural, patient counts, electronic medical records, etc. However, this requires a significant investment that emerging pharma companies with smaller budgets often can't afford. Further, a company rarely needs all these data sources. Instead, emerging pharmas should scrutinize their needs and purchase the data that will best help them address those needs. They should also look to supplement syndicated data with publicly available data, such as open payments or census data, when appropriate. The data required for launch will vary depending on therapy area, but the approach will be the same.

If an emerging pharma company is launching a first-of-its-kind product, it may not have any historical market data. But that doesn't mean it has to operate in the blind. The commercial team should reference data on patient comorbidities and use its knowledge of the patient journey to identify potential analog products and markers of potential. Finally, it's crucial to refresh data just prior to a product launch. For example, the commercial team should refresh market data six to eight weeks prior to product launch to make sure the company's deployment, forecasting, and targeting align with current market conditions.

Focus on flexibility. Commercial teams should plan for a variety of "what-if" scenarios prior to launch. For example, what if a sales territory or team over- or underperforms dramatically? How will that impact payouts for the field sales representatives and total company exposure? If a company analyzes various possible outcomes before launch, it can adjust its commercial tactics and parameters to avert disasters like a demotivated sales force or financially ruinous compensation plan.

An emerging pharma company also needs to ensure the technology solutions it implements to help organize and analyze large amounts of data can facilitate a flexible approach to launch. Many startup commercial leaders make a mistake by buying big-name solutions that do much more than their company needs. These solutions, while robust and comprehensive, can require significant effort to implement and maintain. Therefore, they aren't always the best fit for emerging pharma companies, which typically need more configurable solutions that allow for quick customizations and changes.

— Erik Cruz is a Manager at Beghou Consulting


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The State of Cross-Border Funding in the Life Sciences

Record capital flows across global public and private markets has opened up new channels of investment in early-stage and novel science

By James Leech

The biotechnology ecosystem has seen considerable investment over the last few years from a multitude of sources within both the private and public markets. Traditional legacy investment funds are continuing to invest heavily in the sector, with multiple well-known venture and growth equity firms raising new funds well beyond their target size and many new first-time fund entrants joining the mix. Beyond these traditional early-stage investor types, multiple prominent asset managers (i.e., Baillie Gifford, crossover funds, hedge funds, and sovereign wealth funds) have been lured into the life sciences ecosystem as a means of generating alpha after observing high profile exits from the sidelines for many years.

The US is fertile territory for identifying investable opportunities within the life sciences and a prominent target capital source for emerging companies (see Figure 1 on page 32). However, there has been a considerable increase in cross-border funding activity as globalization continues at a macro level and regional interest in novel drug and device development to address both economic and social needs and broad recognition of the scientific breakthroughs occurring all over the world increases.

The private financing market is the lifeblood of the life sciences sector. In 2018, the market has already seen a record number of private venture financings, with US life science companies securing a staggering $4.7 billion in funding in the first three months alone. This level of funding is almost four times the average amount raised in the same period during 2012 and 2013. We believe this is occurring for reasons beyond merely the high number of promising life science companies that continue to emerge.

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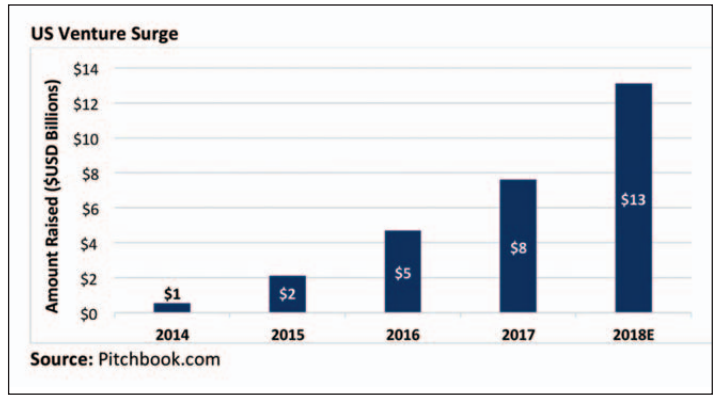

Figure 1. The amount, in billions, raised in US life science venture rounds (2014 to 2018 annualized).

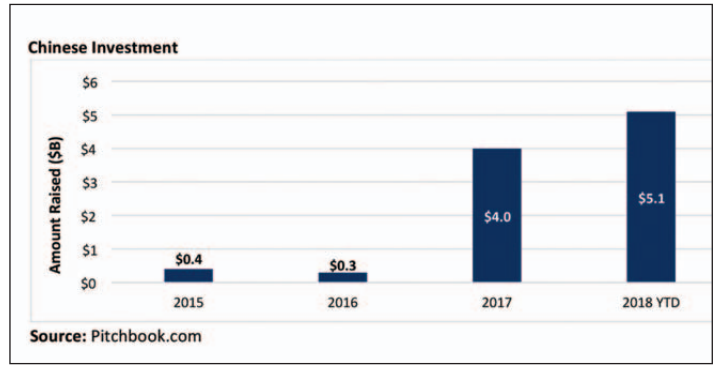

Figure 2. The amount, in billions, raised in funding rounds involving Chinese Investors.

Over the last year, we observed several new investor-type entrants to the early-stage life sciences field, with public crossover investors, non-US venture funds, sovereign wealth funds, and high net worth (HNW) family offices eyeing a piece of opportunities for the first time that may turn out to lead to highly lucrative exits.

China-based VCs and HNWs have put a record amount of capital to work for US-based life science companies. Chinese VC investment into US biotech companies in the first half of the year surpassed the record set for the whole of 2017, with these funds participating in investment rounds in US biotech companies worth $5.1 billion so far (see Figure 2). We believe that these capital flows into US biotech from China will continue at a record pace. Chinese healthcare VC and PE funds raised $40 billion last year, but invested just $12 billion domestically, according to ChinaBio.

There is a significant disparity in the amount of venture funding raised by companies depending on their region of origin. In 2015, there were roughly an equivalent number of life science organizations raising capital in the US vs. the EU. However, the US financings outpaced the EU financings six to one when considering dollars raised (see Figure 3 on page 49). This is a function of a number of factors, including:

1. There is less institutional capital available to emerging life science companies in the EU.

2. EU-based companies are considerably more capital efficient, often approaching financing through drip feeding rather than the buffered capital approach.

3. EU-based companies take a more pragmatic and risk-averse approach to drug development (i.e., generating proof of concept in one to two target indications versus pursuing five to 10 at once).

Life science transaction advisors widely believe that truly innovative and high-quality companies will always find a way to attract the capital needed to further their R&D ambitions. In recognition of the significant regional funding gap highlighted, several EU companies are now looking to US private funding sources as a means of increasing their capital base. Additionally, EU government organizations and venture syndicates are urging sources of capital from non-EU regions to fund their companies. This cross-border funding ambition for US venture dollars extends in both directions.

As record-breaking life science focused venture funds were raised within the US, there are a high amount of dollars competing for high-quality US investment opportunities. This dynamic has lowered the cost of capital to those seeking funding and, in turn, has led to an increase in valuations during these funding rounds (i.e., venture investors are paying more money for ownership stakes than before).

The US has historically been regarded as the most attractive target for life science companies seeking to raise capital via the public equity markets. Over the last four and a half years, 225 life

Continued on Page 49

The Pulse of Biopharma M&A

Promise, cautions in life sciences dealmaking spotlighted

By Michelle Maskaly

M&A-driven dealmaking in 2018 across the biopharmaceutical industry is on track to becoming the second highest of the decade.

"There's been a significant increase in private financing, principally driven by Series A financing, which tells us that new company formation has accelerated in the last four to five years," says Neel Patel, managing director, commercial strategy and planning, at Syneos Health Consulting, and co-author of the 2018 Dealmakers' Intention Study. Released in June at the BIO International Convention in Boston, the study, now in its 10th year, showed a mostly healthy landscape for prospective buyers and sellers, with Patel noting, "dealmaking in the life sciences is continuing an unprecedented run."

"Licensing and M&A will likely experience a significant increase in activity as US tax reform will increase the amount of capital buyers have available for assets/partnerships," he says. "Private financing's bull-run will continue as life science investors have recently closed new funds for investments and many are out actively fundraising now."

Hot spots

Oncology remains the top therapeutic area of interest for buyers and sellers, and the supply surplus in this segment stood out in this year's report. "Compared to 2017, oncology has become a much more attractive, opportunistic market for buyers, suggesting that premiums could start seeing a potential decline in the coming year for products that are not highly differentiated," says Patel.

He explains that larger companies have narrowed their focus, and fewer are fully focused on oncology. "For sellers, this means they have to be very mindful about differentiating their asset and making sure the core mechanics of commercial success are being considered—things like patient population targeting, making sure you can demonstrate that stakeholders' most important unmet needs are being addressed with the data you are generating and that you're not just another "me too" in the marketplace," says Patel.

According to the report, other areas of high demand include hematology, respiratory/pulmonary, and renal assets. The top-five areas for licensing include immuno-oncology, CAR-T cell therapy, CRISPR/Cas9, microbiome, and cancer vaccines.

Red flags

There are some trends that Patel says leaders do need to be cautious about. "In addition to the greater surplus in oncology assets, we also saw that it is becoming much harder to close deals," he says. "The overall deal conversion rate fell to 1.9% in 2017 from the more typical 5% range. This was especially the case at later stages of the deal, after progression to CDA, with lower conversions to term sheet—a warning to sellers to be vigilant and responsive until the deal is actually signed." The report also showed a greater parity in the discount rate between buyer and seller—both at 17% compared to the 4% that was seen in 2017. "This could suggest an increase in partnerships as opposed to outright acquisitions—again, an indication that buyers are looking to structure deals where the sellers participate in some of the risk, and that sellers are assigning high valuations to their assets compared to 2017," explains Patel.

The IPO question

The IPO outlook appears mixed. "The year-to-date pace of IPOs indicate that 2018 financing raised in the IPO market to be around the average of the five-year trend, with expected volume of just over $2.5 billion—a relatively strong environment compared to historical standards," says Patel. However, he did add, "we are also seeing a large increase in Series D+ financing, indicating that many companies are opting to stay private longer to avoid an IPO and develop their pipeline to meaningful value inflection points or commercialize themselves."

Retrospective

With 10 years of data to look back on, Patel is able to take an extensive look at the dealmaking landscape and draw some solid conclusions. "One of the most interesting changes we've seen in the study over time has been the increased fragmentation in the industry, with more and more smaller companies holding onto assets longer or even 'going it alone' to commercialize assets themselves," he says. "In large part, this is thanks to the robust financing environment and the exponential increase in financing options available to emerging companies." PE

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PORTUGAL

TURNING THE PAGE

Portugal experienced the best economic growth in a decade in 2017, up 1.2 percent on the previous year to 2.9 percent, and the Bank of Portugal reports 2018 will see 2.8 percent growth. Adalberto Campos Fernandes, the minister of health, comments "We are performing favorably; we see remarkable GDP growth, low rates of unemployment and enjoy a more stable budget (…) These steps forward contrast sharply with the difficult period between 2011-2014."

Further evidence of an economic revival includes healthcare spending growing to 8.9 percent of GDP—which lags behind more developed EU economies such as France and Switzerland but aligns closely with Northern Europe and Scandinavia. Manuel Heitor, the minister of science and technology, explains that the entire life sciences sector stands to benefit, and a change in strategy will drive progress in science. "Portugal has since diverged from the European averages to show an increase in R&D and innovation. The official data is clear; public expenditure in R&D increased by EUR 40 million (USD 46 million) last year, and private spending increased by EUR 90 million (USD 105 million)." Critics explain that the resurgence is primarily due to continued favorable international investment conditions, whereby fiscal incentives, a highly skilled talent pool and a good quality of life have attracted foreign investment and increased private sector consumption.

This sponsored supplement was produced by Focus Reports
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Cover pic ©: Nadir Afonso

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PHARMA FOOTS THE BILL

While Portugal exited its bailout programme in May 2014 without the need for a new financial package, government austerity measures curbed pharmaceutical reimbursement, and pharmaceutical companies made a display of solidarity. The executive director of APIFARMA, the Portuguese industry association for innovative medicine companies, Heitor Costa, explains how pharmaceutical companies collaborated with the government by agreeing to a market cap, and they now intend to regain their former position: "Following the crisis, Troika's restrictions sought to downsize the market. However, since Portugal exited Troika, we no longer battle with these measures. The testament to our long history of co-operation with government and stakeholders was made clear in 2016, upon signing on an agreement that no longer features a cap. The agreement established rational market developments, and as such, we pay a contribution to the system's sustainability – similar to a tax – and for the past two years, we have seen steady growth."

Nonetheless, following the crisis, several companies found managing an affiliate in Lisbon a Sisyphean task in the face of the government's decision to cut pharmaceutical costs. Of the Top 100 pharmaceutical companies in Portugal, over 15 pharma

Adalberto Campos Fernandes, minister of health; Manuel Heitor, minister of science, technology and higher education; Heitor Costa, executive director, Apifarma

MNCs have effectively withdrawn from Portugal to establish Iberian headquarters across the border in Madrid, Spain. Nelson Pires, general manager for Portugal, the UK, and Ireland at Jaba Recordati, explains "the 'Iberianization' of Portugal is a serious risk which undermines the relevance of the Portuguese market for European affiliates." Salvador Lopez, general manager of Mundipharma, comments that "In 2014, Mundipharma confronted a challenging market that had been heavily impacted by the Troika economic crisis; the healthcare system, in particular, faced many constraints."

Numerous commentators agree that Portugal's economic revival is yet to impact the pharmaceutical industry. Antonio

Leão, general manager for Lilly, acknowledges that although the outlook is promising, there is still much to be done. "The total market is worth roughly EUR 2.9 billion (USD 3.4 billion), and if we look back to the crisis period, the retail market was severely hit and lost approximately a third of its total value. Only now is it starting to regain some of what has been lost."

THE TROIKA EFFECT

The brunt of this economic impact was not confined to the pharmaceutical sphere; from medical devices to contract research organizations (CROs), the Troika intervention sparked a chain reaction of challenges across healthcare. Antonio Cabral, general manager of Medicinalia Cormedica, one of the most significant Portuguese medical devices company, notes that "We have excellent doctors, nurses and healthcare professionals but sometimes we lag behind in the delivery of sophisticated medical devices, which is exacerbated by our recent exit from the economic difficulties." Maria Queiroz, CEO of Eurotrials, a Portuguese homegrown CRO, comments that "During the crisis, the national healthcare system and physicians felt the pressure to be 300 percent focused on patients and patient evaluations, and naturally, research efforts took a back-seat role. As we exit the crisis, the physicians' gaze will once again turn to the importance of translational research and clinical trials."



Nelson Pires, general manager, Jaba Recordati; Antonio Leão, country manager, Lilly; Antonio Cabral, general manager, Medicinalia Cormedica

José Aranda da Silva, a key opinion leader and the first president of INFARMED in 1993 offers a balanced view: "The crisis had a huge impact on the healthcare sector, and between 2009 and 2015 Portugal experienced cuts of around 30 percent. However, the country is now recovering strongly, and the healthcare budget is beginning to grow. Unfortunately, this success is not enough, and there is a consensus among many politicians who believe that the amount of money allocated to healthcare needs to increase." The debate continues



José Aranda da Silva, president, health and national health service foundation; Antonio Portela, CEO, Bial; Filipa Costa, general manager, Janssen

as pharmaceutical companies wait with baited breath to reap the rewards of their collaborative efforts from 2011 to 2015. Although an economic revival is underway, there is a long way to go before the pharmaceutical landscape will realize the benefit. In the meantime, Antonio Portela, the third generation of the Portela family to manage Portugal's leading pharmaceutical company, Bial, argues that the onus is on pharmaceutical companies to take the initiative and drive change: "We, as an industry, must attract venture capitalists to consider Portugal, but they will only do that if market conditions are attractive: if prices, timelines, and payments are competitive on the European standing."

While Portugal experiences a revival, challenges to the pharmaceutical industry take on many forms, from a chronically underfunded healthcare system to a rise in generic penetration, to tackling more market access hurdles than many other Mediterranean countries could handle. As Filipa Costa, country manager from Janssen comments, " If we consider the portfolio, the European medicines are generally made available in Portugal, although sadly there is a considerable delay in market access relative to other European countries. The time taken from EMA approval to access in Portugal, (granted by INFARMED), to hospitals (which have their autonomous procedures), is closer to the two-year mark than the legislated 200 days."

GENERICS TO THE RESCUE

The healthcare market dynamics have shifted away from a brand-oriented market, whereby healthcare professionals prescribed more originator drugs, leading to an increase in generic consumption. The share of generics has risen from 45 to 49 percent penetration in the past three years, and the trend looks to continue. Paulo Lilaia, the President of APOGEN, the Portuguese Generic and Biosimilar Association and CEO for Generis, a local generics company acquired by Aurobindo in 2017 conveys, "The generics and biosimilars role in the healthcare system

TOP 20 PHARMA COMPANIES IN PORTUGAL

(MAT MARCH 2018)

		SALES (EUR)	MARKET SHARE
	TOTAL	2,751,203,489	100.0%
1	MSD	147,595,183	5.4%
2	MYLAN	127,228,600	4.6%
3	BAYER	118,775,655	4.3%
4	TEVA	117,285,083	4.3%
5	SANOFI	108,858,316	4.0%
6	ASTRAZENECA	108,800,505	4.0%
7	NOVARTIS FARMA	101,374,831	3.7%
8	GLAXOSMITHKLINE	97,455,921	3.5%
9	GENERIS	86,725,237	3.2%
10	BIAL	86,386,754	3.1%
11	BOEHRINGER INGELHEIM	76,250,736	2.8%
12	SERVIER	72,947,198	2.7%
13	MERCK SA	63,006,792	2.3%
14	PFIZER	60,400,406	2.2%
15	TECNIGEN	55,015,031	2.0%
16	JABA RECORDATI	48,761,334	1.8%
17	MENARINI	48,554,457	1.8%
18	GSK CONSUMER HEALTHCARE	48,130,550	1.7%
19	JANSSEN	44,586,362	1.6%
20	MEDINFAR	44,186,190	1.6%

Source: Health Market Research (HMR)

is vital: if we want to treat more patients with better value-added medicines, we have to economize in other areas. Generics create the necessary room to have money for investments in new and innovative products."

João Madeira, the experienced country manager for Mylan, comments "Portugal lacks the resources to treat as many patients as needed in the right timeframe and with the right product, so we need to make more efficient use of the available resources." In essence, prioritizing the generic medicine over the innovator following patent expiration saves money for the healthcare system. Mario Madeira, from a rival generic-innovator hybrid company, Teva, agrees that "The generics strategy paves the way for access to affordable medicines for healthcare professionals and patients." The strategy for rising generic penetration must stay the course, however, because as Madeira continues: "If we open room for doubt, we will never eradicate the stigma that still purveys in some regions of the market that says that 'generics are not as good as branded medicines.' Although the mindset has evolved, and it is far away from a total misunderstanding, today Portuguese people embrace generics, and the uptake is faster than it used to be. Today, we can confidently say that most Portuguese patients are treated with a generic medicine."



Paulo Lilaia, CEO, Generis; João Madeira, country manager, Mylan; Mario Madeira, general manager, Teva

Now with almost 50 percent market share, generics are one of the cornerstones of the Portuguese pharmaceutical market's development. According to APIFARMA's Costa, given the nature of the healthcare system, "The more generics present in the market; the more innovations have room to develop," especially because greater generic medicine usage frees up resources to be spent on reimbursement. There is one important caveat: "The golden rule with regards to generics is that we must respect patents and intellectual property; this is a non-negotiable red line for APIFARMA. If intellectual property rights are respected, then we allow room for innovation which is crucial to the healthcare system's success."

FREEING UP FUNDING FOR INNOVATION?

For Jaba Recordati's Pires, the solution is to "have a foot in both camps; generics and innovatives, then we can represent a complete solution to patients that requires more than just the monotherapy." RJ Lasek, former country manager for Takeda, (now vice-president, commercial planning, and pricing) outlines his ideal strategy in the face of a rising generic tide: "As a government partner, we want them to be able to manage the category better and improve patient outcomes. Consequently, we insisted that the innovation we offer is priced in a way that will enhance the government's overall cost per outcome. The trick is to strike a balance between innovation, biosimilars (or generics), and collaborate with the government. The government is open to this kind of debate, and there is room for innovation."

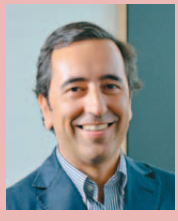
The introduction of biosimilars to the market from companies including Mylan, Amgen, Mundipharma and Teva will reinforce efforts to allocate more resources to value-added medicines. APOGEN's Lilai continues adding that "Although biosimilars require significant amounts of investment, they are a crucial part of generic pharmaceutical companies' business given the potential they represent." Mylan's Madeira mirrors this view, "The biosimilar business brings value to the national health system so that, with the same budget, it can treat more patients and at an earlier stage of the diseases."

RJ Lasek, country head, Takeda

José Aranda da Silva paints a detailed picture of the generic landscape in Portugal: "In the beginning, it was not easy for the system and for companies to adapt to this change in market dynamics. Nonetheless, most of the international companies have since entered the generics market, for example, Novartis and Pfizer; and we should see more companies like this entering Portugal. Generics will continue to grow." Overall, the increase in generic consumption and the arrival of biosimilars have granted the authorities the necessary breathing space to improve drug access, better target non-communicable diseases, and balance healthcare expenditure.

The Portuguese Flagbearers

Sérgio Luciano, CEO, Quilaban



Paulo Barradas Rebelo, CEO, Bluepharma

For local companies, the trick is to keep things simple in the face of numerous challenges and at times, high levels of bureaucracy. At Basi laboratories, a local success story led by Joaquim Matos Chaves, he often jokes that "I spend half my time insisting that people do not complicate procedures in Europe; if we keep things simple and focus on the vision of the product, then success is far more likely." Basi Laboratories recently received a EUR 40 million (USD 47 million) investment as part of Horizon 2020, which looks to "increase production output from four million units to roughly 100 million. For a small company, this is a vast increase in production." Indeed, Matos Chaves's ambitious vision is "to bring product manufacturing in line with prices in Indo-China." Intrinsic to this vision is an internationalization trajectory that expands from PALOPs countries (the group of Portuguese-speaking African countries), to as far afield as "the CIS, the Middle East, and French-speaking African countries." Sérgio Luciano, CEO for local diagnostics company, Quilaban, explains the usual route for ambitious Portuguese companies "our international expansion started by the African Portuguese speaking countries, namely into Angola and later on into Mozambique, Cape Verde and Guinea Bissau, given the convenience of shared language."

Basi Laboratories New Facilities

Bial exemplifies the need for Portuguese companies to create scale. Portela has "in the past five years, switched turnover from 70 percent domestic, 30 percent international to 70 percent worldwide, 30 percent Portugal." Bluepharma, a rival manufacturing company based in Coimbra, (Portugal's third city after Lisbon and Porto), also has plans to expand, as Paulo Barradas Rebelo, CEO looks to invest 15 million into a new industrial unit. "Our business in Portugal is small but important because this is where we see our portfolio app and flow and where we can train and learn new businesses before exporting to larger markets." There are opportunities to be had in Portugal, but the critical mark of a local company's success is international expansion.

For Basi, who has just received "the most significant investment that the pharmaceutical industry in Portugal has seen in recent years, and we are the first mid-cap sized Portuguese company to receive funding from EIB," international expansion and "being one of the reference manufacturers of choice in Europe," is an attainable goal.

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THE MARKET ACCESS MAZE

In light of an increased generic market share, one would assume that innovative companies across Portugal are reaping the rewards, undoubtedly enjoying the allocation of more resources while relishing faster approval times. In the period between 2016 and 2017, the Ministry of Health approved more than 120 innovative drugs in areas including oncology, HIV, and rare diseases. Costa from APIFARMA puts this statistic into context, "the government has approved more innovative medicines in the past two years than the combined total reached during the period from 2010-2015; 60 in 2017 and 51 in 2016."

Maria do Céu Machado, president, Infarmed

Moreover, new regulation put forward by INFARMED – Portugal's medicines regulator – has drastically decreased approval times for drugs. Under the direction of Maria do Ceu Machado, INFARMED president, SiNATS (the national evaluation system for health technologies – Portugal's Health Technology Assesement (HTA) organization), now approves generic medications within 30 days and prescription innovation within 90. Machado comments that INFARMED is dedicated to improving Portugal's poor reimbursement reputation and seeks to bring down the 300-day average, "SiNATS was reviewed in September 2017, and the new evaluation deadlines were established: generics would follow a 30-day deadline, and new molecules would be brought to market in less than 180 days." It would appear that the authorities have responded to the industry's valiant displays of collaborative assistance and support during the crisis.

Indeed, the dialogue is productive and welcome by both interlocutors, the industry, and the authorities. As Mylan's Madeira highlights, "the authorities are always open to identifying efficiency areas where costs can be optimized so that we can provide better offers for unmet needs." Madeira echoes comments made by Alicia Folgueira López, country manager for Portugal and Spain for up and coming rare diseases company Alnylam, "the government is open to discussion and willing to implement ideas put forward by the industry." From the other side of the equation, the minister of health points out that "the government has an excellent strategic relationship with pharmaceutical companies."

LITTLE RESPITE FOR THE WEARY

Nevertheless, as the old Portuguese adage goes, "Vai muito do dizer ao fazer" - "There's a long way from saying to doing." Despite excellent dialogue and young reforms teeing up a promise of faster approval times for medication, industry players are tentative in their reception of market access reforms for two principal reasons. One, Portugal is historically a slow market access country; and two, the timelines for the new evaluation are not yet complete. Bial's Portela succinctly explains, "in Portugal, one of the consequences of the crisis is that processes are slow, in some cases approvals and pricing can take around 300 days. We as a country are improving, and I hope that this can allow patients to access medicines earlier on." Nelson Pires from Jaba Recordati agrees that "The new president has increased the number of approvals for new drugs, but we cannot forget that we are still one of the slowest countries in Europe—we recently saw that the only country that is slower than Portugal is Bulgaria." Lilly's Leão chimes in, "The new law states that drugs must be evaluated in 180 days, plus 30 business days for contract negotiation. All in all, this adds up to a stipulated approval period of roughly eight months. It remains to be seen the real impact of these changes" given that the reform's implementation took place in late 2017 and features a six-month evaluation deadline.

From specialists in diabetes to pharmaceutical market leaders, despite relative improvements and much discussion on the subject, no one can escape the delays. Janssen's Filipa Costa sheds light on the depth of the situation: "sadly there is a considerable delay in market access relative to other European countries. The time taken from EMA approval to access in Portugal, (granted by INFARMED), to hospitals (which have their autonomous procedures), is closer to the two-year mark than the legislated 200 days. INFARMED's analysis of new medicines is thorough, complete and provides a sound understanding of innovative treatments. The issue is the lack of transparency and agility on offer during the process. The new president of INFARMED has made a positive impact in increasing transparency, however changing a public institution does not happen overnight." Mundipharma's Salvador Lopez concurs; "we see fantastic progress in facilitating access, although we still face an uphill climb in ensuring that more drugs are reimbursed efficiently. The time constraints hinder progression and stifle innovation."

For many pharmaceutical companies, delays are a source of complaint; curiously, however, Florian Ibe, general manager at Bayer, explains that these delays can also offer learning opportunities: "On the positive side, the delay allows us to learn from other markets and tailor our educational efforts to these learnings. This includes patient identification, side effect management, and patient counseling, among others." For a multinational company, observing the approval route for faster neighboring companies for a drug can speed up processes for the medication post approval in Portugal. Still, Ibe understands that "it is difficult to have less predictability on drug spend, but we argue in favor of changing the way we think about and discuss financing of drugs."

NOT ALL FADO

There are more pockets of optimism to be found on the Westernmost European coast. Recordati's Pires points out: "INFARMED recently carried out an excellent inquiry that projects long-term into understanding the pharmaceutical industry. It sought to understand the new molecules that will be brought into the market until 2020. Therefore, the authorities can comprehend the risk of future costs; a smart move! We welcome this approach, as opposed to focusing on year by year solutions in healthcare." Nevertheless, the global consensus is clear; government and industry agree that progress and decision-making are slow. For Takeda's Lasek, "The Ministry commits to improving innovation, but the process is slow," and for INFARMED's Machado, "The system is incredibly complex."

Salvador Lopez Orland, general manager, Mundipharma; Florian Ibe, managing director, Bayer

For those sat around the table during the industry and authorities' discussion on market access, the implementation of transparency, agility and a long-term vision appear to be the logical solution. Costa's Jansenn suggests that "conversations are more accessible than email exchanges, and dialogue catalyzes efficiency." Moreover, Lilly's Leão infers the result of these improvements, "Eliminating barriers and increasing transparency would mean that our patients receive innovation at the same time as our neighboring countries across Europe." Moreover, it is, in fact, the proximity of the industry to the authorities that help drive forward discussion and inspire action. "The advantage in Portugal is that you can get to grips with the problem and get to the root of the matter more efficiently, and new GMs, for instance, are in closer contact with KoLs, stakeholders, and


Rui Ferreira Dos Santos, country manager, Almirall; João Norte, CEO, HMR

managers across the country," observes Rui Santos, general manager for Almirall.

Conversely for research operations, the tight-knitted and cliquey nature of the pharmaceutical market can create difficulties sprouting from regionalism. João Norte, CEO for HMR, a budding homegrown market research specialist articulates, "minor regionalism is a small geographical barrier, and Portugal is so centralized that at times, the excellent research located in one specific city might not try to connect with another city." Antonio Cabral, from Medicinalia Cormedica explains further, "The route to market in Portugal is quick and the population is small. One limitation we find is the difficulty we sometimes have to explain the cultural needs and particularities we face in our Portuguese market."

Requests for increased transparency comes from both parties, however, as INFARMED articulates that "the issue we confront on a daily basis is the lack of visibility on pharmaceutical companies' pipelines before they submit their dossiers. If we had eyes on these strategies, we would be able to better prepare for the arrival of these drugs. We must strive for collaboration between companies and governments." Moving forward, Mundipharma's Lopez underlines the need for collaboration: "We – authorities and industry – should partner more to shorten the time to the patient of innovative drugs as they have proven the benefits for patients and the sustainability of the health system."

Filipe Assoreira, President, and José Albuquerque, secretary general of P-Bio, the Biotechnology Industry Organization, have the last word on the matter, "in comparison to our neighboring countries, there is a message of hope! Despite the financial crisis we have had all over Europe, we continue to have the same positive pattern showing that this sector is moving forward." Recordati's Pires is equally optimistic, "Despite market access difficulties, price squeezing and the increase in generics, we can still bring added value to the market through our high-quality products." With market access reforms soon to bear fruit, productive debate around the table and a strong sense of collaboration following years of solidarity, the Portuguese pharmaceutical landscape is turning the page.

PILOT PORTUGAL

Traditionally, Portugal has a reputation for being an innovator and a worldwide first mover. One of the first Western European countries to make e-prescriptions mandatory in 2011, the second country worldwide after Canada to introduce an HTA (SiNATS), and in 2001, in the face of a heroin crisis, Portugal became the first country worldwide to treat possession of small quantities of drugs as a public health issue, as opposed to a criminal matter. This creative and out-of-the-box thinking nature manifests itself in the life sciences, where Portugal is the benchmark for healthcare digitalization in Southern Europe, and both the talent pool and the infrastructure combine to create an attractive setting for the trial of new ideas in a controlled, well-prepared environment, that has adequate tools and flexibility to find solutions.

The industry and government alike have cottoned onto Portugal's potential to be Europe's laboratory, as Ana Teresa Lehman, secretary of state for health explains: "We are a small country, but we are highly-developed and ready for new technology; indeed, we are a fertile ground for experimentation and a test-bed for tomorrow's technology. Our crucial policy is to prioritize innovation through experimentation which will drive growth across the industry." Moreover, for Novartis country president, Cristina Campos, "Novartis has the right ecosystem in Portugal for trying new models and approaches."

A fellow first-time country manager Alnylam's López points out that "In Portugal, the system is incredibly centralized whereas Spain is renowned for its decentralized processes. Portugal is an exciting country to develop commercially because it is well organized in reference centers." Janssen's Costa justifies that "more and more companies begin to see the value of testing out new and digital ideas because of the mitigated risk associated with our relative size and expertise in complex fields," and finally, Filipe Paias, general manager for Baxter agrees, "Portugal is a fantastic pilot country. The way that we overcome these challenges can be the benchmark for bigger countries. We can therefore test and mitigate part of the solution in Portugal, a smaller market, before translation to larger economies."

HANDLE WITH CARE

Despite this situation, for Mylan's Madeira it is this idea of mitigating the risk that could be harmful to Portugal's future. "There are two schools of thought pertaining to Portugal's perception as a testbed or pilot country. The wrong one is to consider and insinuate that we can test anything in Portugal at low risk because the patient pool and mechanisms in place in Portugal allow for fewer patients to suffer. We must avoid treating or thinking of Portugal as a crash test dummy because Portugal is one of the fastest growing economies in the mature European marketplace." Filipe Novais, country manager for Astellas, bolsters the argument explaining that

Filipe Assoreira, president, P-bio; José Albuquerque, secretary general, P-bio; Ana Teresa Lehmann, secretary of state for industry

Big Pharma must foster safe practices and welcome the right innovation, "The Portuguese population is eager for innovation, and as part of the European Union, and given our size and expertise in science, we are a safe environment for new practices and innovation." Baxter's Paias notes that "the Portuguese have built up a reputation for being a country where fading ideas are given new life."

Not only are pharmaceutical multinationals alert to Portugal's potential to become the yardstick for operations elsewhere, but market research and digital health IT companies confirm the concept. HMR's João Norte comments that "As we are exposed to more and more countries in Europe, we

Filipe Paias, general manager, Baxter

Filipe Novais, country manager, Astellas

become more aware that Portugal has an excellent base for the translation of ideas. We have a unique national healthcare system that is universal, free and crucially, heavily digitalized."

GOING DIGITAL

Similar to many Western Economies, Portugal is attempting to embrace digitalization in healthcare, but unlike Europe's Big Five which struggle due to huge populations and decentralized systems, thanks to Portugal's size and tech-savvy population, industry players and authorities have found success in implementing nationwide digital projects.

Portugal is making a noble effort to remove paper, effectively entirely digitizing the healthcare system. As many as 92 percent of patients leave a medical appointment without a paper prescription, and as HMR's João Norte goes on to say: "we benefit from a high level of digitalization in the country; we can be a hub for Europe to create real-world evidence."

The Ministry of Health employs a dedicated team to roll-out tech services in healthcare. Henrique Martins, CEO of SPMS, (the Ministry of Health's Shared Services organization), explains "Portugal is unique in Europe as it has electronic health records designed by the government in primary care and hospitals. The software hospitals use for most functions (admitting a patient, documentation, discharge) are produced by SPMS's team."

Joaquim Cunha, executive director for Health Cluster Portugal, a private, non-profit organization dedicated to the consolidation of Portugal's healthcare industry, says that "the intelligent use of ICT is one of the most powerful and efficient answers to some of the major challenges we have ahead in health research, management, and treatment."

LEADING BY E-XAMPLE

Portugal has hosted the international Web Summit since 2016, a technology conference attended by 60,000 CEOs, founders of tech startups and stakeholders working in the global technology and related industries. And in 2018, Lisbon's Altice Arena also hosted the second eHealth summit, focusing on digital

Introducing Alnylam: A rare diseases authority

Alicia Folgueira López, country manager, Alnylam

Alnylam, pioneers in the RNA interference field, seek to bring their revolutionary medicine across Europe, and in particular, Portugal before 2020.

The affiliate is only a year old, how has the global vision trickled down into Portugal?

I was the first Iberian employee for Spain and Portugal, and we began from scratch – without an office or employees—it was an adventure, and it continues to be so. We now have nine employees with at least double figures by the end of 2018.

What is the significance of Portugal for Alnylam?

Portugal will be at the center of the strategy globally—the eye of the hurricane—because it is the most common country worldwide for ADD disease. There are five times the number of patients in Spain for the same condition.

How does Alnylam observe the environment for diagnosis?

Diagnosis is always a challenge, and as a stakeholder in the rare diseases community we must improve the diagnostic process and reduce the time to diagnosis. The most important day in the life of a registered patient is the day that the patient finally understands what disease he or she suffers from.

transformation in healthcare. Direct consequences of international influence in tech ventures are easy to spot; the country is teeming with healthcare startups and has seen the number of life sciences startups triple between 2008 to 2015 according to Labiotech's calucations.

The minister of health comments that "we are now living in an age where digitalization, Big Data, the democratization of information and instant access offers enormous opportunities in healthcare, whether it be in patient safety, scientific activity or in innovation." The minister for science, technology and higher education equally features digitalization as a priority, "we seek to promote digital skills. In all areas of the economy and society, and especially within the health sector, we have launched a national initiative to foster digital skills, INCoDe2030."

Private industry will both benefit and improve upon gains in the digital health world. For Cerner's Jorge Sequeira, Portugal is the perfect place to introduce the "next generation of EMR (electronic medical records), to the market." Plus, "From clinical stakeholders to software engineers, we observe a strong will to make progress, and a trend for high adoption rates of new technology from the Portuguese population. Indeed, the Portuguese are renowned for being tech-focused, for example, if we consider the new generation of nursing whereby professionals seek fast adoption of technology."

Henrique Martins, CEO, SPMS; Joaquim Cunha, executive director, Health Cluster; Maria João Queiroz, global CEO, Eurotrials

SOURCING TALENT: ROUND PEGS IN ROUND HOLES

Not only are the Portuguese future-focused, embracing digital technology across the nation, but they are well-prepared, well-qualified, "and as an added value, the Portuguese speak fluent English" says Eurotrials' Queiroz. Foreign general managers are keen to highlight the Portuguese work ethic, RJ Lasek from Takeda comments that the Portuguese "are 'buttoned-up' in that they are focused, professional, and committed. They see the importance of their job and the earnest responsibility it entails."

Local Portuguese pharmaceutical executives comment on the strength of human prowess in their affiliates: Novartis' Campos comments that: "Novartis Portugal is also seen globally as a talent machine; we export many talents and even the talents and capabilities that are not exported often contribute to projects beyond Portugal." Lilly's Leão, a fellow Portuguese, confirms the Portuguese prowess "We may not have as much money as the big five, but when you consider (the people's) flexibility, resilience, creativity, and overall capabilities, the Portuguese affiliate is an attractive and growth-oriented affiliate."

The challenge in managing such a qualified talent pool in a low salaried country is unavoidable. Health Cluster Portugal's Cunha comments that "There are 600+ graduates every year with a PhD in areas related to health and life sciences, which is a significant amount when you look at the small population of Portugal," there is a sincere need to attract talent among pharmaceutical companies and mitigate the risk of a brain drain. He continues "if we do not find occupations for these graduates in the companies (traditionally they were oriented to the public sector), then the R&D system will collapse, and qualified unemployment will start to rise." The Minister of Science and Technology gives credence to this idea that Portugal needs more investment to create work: "We need (more) serious science-based business activities which create the necessary institutional context so that our people do not perform hard work in low-value jobs, and instead, they combine their hard-work with value-added activities."

Cristina Campos, CPO Head and Country President, Novartis

Fortunately, the pharmaceutical companies, many of which are based in the Lagoas Park Business Center in Western Lisbon act as a magnet for young professionals. They regularly win awards, and offer extra perks, development opportunities, flexible working hours and locations to name but a few reasons why they dominate the 'Best Workplaces in Portugal, 2018'. Lopez's Mundipharma affiliate took the Number One spot leading the national ranking among all categories, and nine healthcare and life sciences companies featured in the ranking, higher than any other industry.

Playground for GMs

In light of challenges centered around market access hurdles, bureaucracy, delays and underfunding, Portugal acts as a captivating career destination for pharmaceutical executives looking to carve out their country managing career. Rui Santos, an experienced, Portuguese manager for Almirall, explains that "exposure to these challenges is a fantastic learning platform for a new GM, as although the structure is reflective of big countries, one can familiarize oneself more easily, get to know the ropes and develop, nurturing skills to further one's career in perhaps a bigger market."

For Bayer's Florian Ibe who relishes the challenge in Portugal, "The size and relative importance of the country is perfect for a first-time general manager to embark on their career," and for Janssen's Filipa Costa, "the scale and scope of the Portuguese market make the country attractive to try new ideas, especially for first time general managers. Portugal offers tremendous market access challenges which act as a learning curve for career development. As mentioned, the market is tricky to navigate but that can be a strength for developing one's career and one's resilience." Indeed, for first time general managers, Portugal's market access environment can be the perfect learning platform.

Jaba Recordati's Pires jokes that "If you can succeed in Portugal, you have proved that you can manage the unexpected and therefore can succeed anywhere!" Santos takes it one step further demonstrating that "Starting a career in Portugal is a faster learning curve," but because being a general manager in Portugal involves "living in a warm country with excellent food, wine and a fantastic quality of life, I must warn that these new managers may find it hard to leave!"

THE NEXT CHAPTER...

Jaba Recordati's Pires joins the dots on Portugal's current offering: "We have excellent human resources coming through, and the new generation is quite prepared. I read recently that we have the second country in Europe with MOST PhDs in Europe. We have great fiscal policies for investors looking to move to Portugal. We are one of the most developed IT societies in Europe." Combined with Mylan's Madeira claim that "we are people that are happy to challenge the status quo," Portugal has turned its small size into its strength – as the ideal benchmark for pharmaceutical processes and a creative testing ground, as Baxter's Paias points out, "the Portuguese have built up a reputation for being the country where fading ideas are given new life."

The country has turned its extreme location on the Westernmost border of Europe into an international developmental advantage, Portugal has leveraged an increase in generic penetration to prioritize the better provision of innovation medicine, and it has channeled its tradition of curiosity, audacity and human resources capacity into digital transformation. The one remaining challenge in achieving its potential is "an acute need to tone down the levels of bureaucracy and embrace a more practical, streamlined system," in healthcare, according to Mundipharma's Lopez. Nonetheless, "the market in Portugal offers tremendous potential for rapid and sustainable growth. The affiliate in Portugal is one of the fastest growing in Europe.' Janssen's Costa concludes, "The country has the capability, the workforce and the infrastructure to excel. However, the country is certainly not capturing its full potential."

Continued from Page 32

science firms have executed successful initial public offerings (IPOs) on the two major US exchanges, NASDAQ and NYSE (see Figure 4). We are experiencing a record number of life science IPOs, with 13 completed, raising an aggregate of $3.8 billion in capital in June alone and an additional eight actively in the queue.

Outside the US, exchanges are less attractive for emerging life science companies, with fewer active investors and a less liquid market available to support these high-risk companies. Considering this, it has not been uncommon for high-quality non-US-based companies to target a US listing. From 2014 through July 2018, 37 or 16% of all US IPOs have involved companies based outside of the US.

The inverse of the trend above (i.e., US companies seeking a listing on non-US exchanges) is by and large non-existent. From 2014 to July 2018, just six of the 166 life science IPOs that took place on non-US exchanges involved US-based companies. Of these, four of the listings targeted the London Stock Exchange (LSE), another highly regarded stock exchange that in 2014 was predicted to have a renaissance of biotech IPO listings after Circassia, a UK-based allergy company, raised $330 million in an IPO on the exchange. These predictions have gone unfulfilled, with just 21 life science IPOs completed on the exchange over the last four and a half years. Recently, however, the Hong Kong Stock Exchange has lifted its stringent IPO listing requirements in an effort to attract more companies and open access to the vast amounts of capital in Asia. This change in policy has already created results, with Ascletis achieving a successful listing. There are reports of an additional four companies already eyeing the exchange.

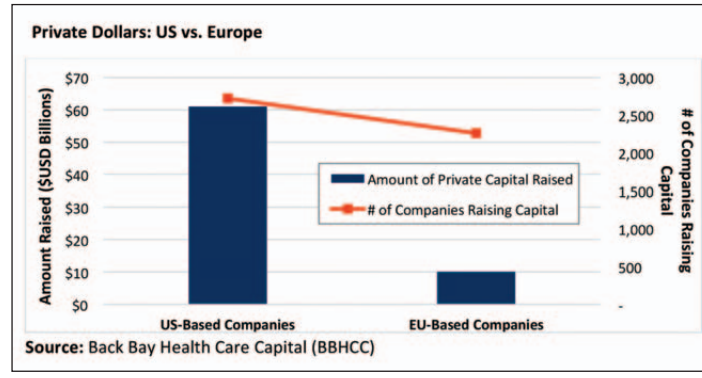

Figure 3. In 2015, the number of companies and dollars raised involving life sciences private financings.

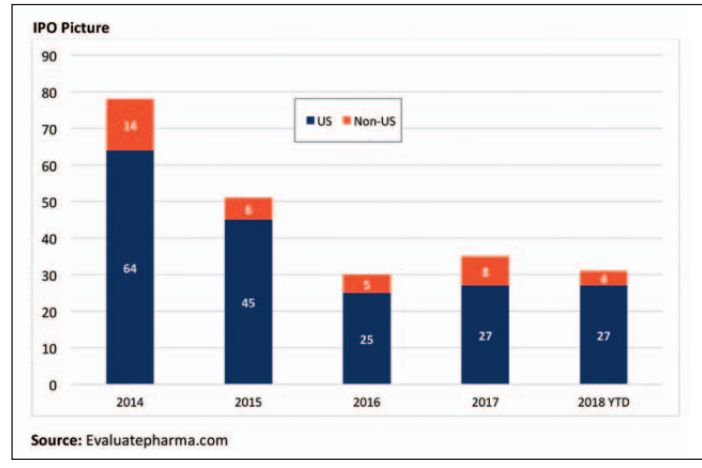

Figure 4. US life science IPOs by company region of origin (2014 to 2018).

Outside the US, exchanges are less attractive for emerging life science companies, with fewer active investors and a less liquid market available

Momentum and migration

It is an exciting time for the life sciences industry, with record capital flows across private and public markets attributed to a myriad of attractive, novel companies and the migration of alternative sources of capital into the field. We expect that recent cross-border funding trends, particularly China investments in US biotech, will continue to experience positive momentum as scientific breakthroughs continue to take place on a global scale and investors seek to participate in their potential success, regardless of their origin. PE

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Traditional Scientific Search is Broken

Using AI to revolutionize research inefficiency

According to market research firm IDC, knowledge workers spend almost nine hours each week searching for information needed for their work. This includes scientists searching for knowledge to advance the development of new drugs, or help identify life-preserving gene therapies, or ensure compliance with the latest regulatory rules. While some scientists may have strategies to manage wading through mountains of documents to find relevant insights, imagine how much more productive they could be if their searches were less time-consuming, more efficient, and cost-effective.

Over the past few decades, the amount of available life science and healthcare information has grown dramatically, paralleling the vast proliferation of high-throughput biology, digital technologies, and online journals. Both life sciences and healthcare sectors encourage the sharing of scientific knowledge and collaboration among researchers. Every year, millions of new documents are published in the form of academic research, patent applications, clinical trial findings, and more. The sheer volume of available data can be overwhelming, even for scientists with very narrow fields of study.

Scientists often struggle to find the answers they need, despite the vast amount of available data. Part of the challenge is the fact that as much as 80% of information is stored in unstructured formats that are difficult to search and analyze using traditional manual methods. By leveraging artificial intelligence (AI)-based technologies such as natural language processing (NLP), users can more easily search through unstructured text sources and find high value, relevant results.

Technical experts vs. self-service queries

Typically, NLP searches require the expertise of technical users to build the queries and extract data insights. While this method can yield excellent results, the technical experts within many organizations are stretched very thin and unable to quickly address the needs of end-users. This means end-users have to resort to their own searches using standard search engines.

Basic search engines, however, are not well-suited for scientific searches. Many lack comprehensive ontologies for key domain concepts, and don't offer NLP-based pattern matching capabilities to effectively surface key relationships between scientific concepts. Users often end up with results that fail to provide direct answers to specific questions. Instead they receive long lists of hyperlinks to full documents with few details about what each document provides in terms of relevant content. Scientists must spend additional hours reading through pages and pages of documents that may or may not provide the answers they're seeking.

Fixing the flawed search process

The inefficiencies of today's search processes limit the ability of life science organizations to increase productivity, speed product time to market, or find hidden nuggets of valuable data. These companies could hire or train new information experts, though it's an expensive and time-consuming option. Alternatively, organizations could empower end-users and equip them with more effective self-service AI-powered search tools that deliver quick and reliable answers to their searches. An intuitive interface that provides access to powerful NLP algorithms and results would allow end-users to use ontologies and find, for example, the key relationships in text that are critical to differentiating between a search for drugs that treat hypertension versus drugs that cause hypertension. The technical experts would then have more time to concentrate on developing the more complex, time-consuming searches.

To make the most positive impact, self-service AI-based search applications must be intuitive and easy to use and have the ability to query unstructured text from a broad set of knowledge resources. The tools must also deliver answers—and not just documents—and provide deep insights from a single search.

The use of AI technologies in end-user applications is growing in retail, banking, travel, and other sectors. But until now, life sciences organizations have lacked adequate self-service AI-tools to facilitate effective searches more broadly across their research teams. By addressing this gap, life science companies have the opportunity to spend less time searching and more time advancing their organizational goals. PE

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