ON THE WORLD STAGE
The Advent of China 2.0 in Biopharma

Xiaobin Wu, general manager of China and president, BeiGene, Ltd., a global developer of molecularly targeted and immuno-oncology drugs.
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Two Steps Forward

**IF I WERE TO BELIEVE** my Chinese zodiac horoscope for 2019, then in the area of career, I’m to expect a “medley of obstacles and conflicts” along my path. First up may be the choice of China as the focus for this issue. It seemed a fine selection based on all the positive press around biotechs in the country, as well as notable regulatory developments. But then came a couple of manufacturing scandals, including improperly prepared DTaP vaccines, followed by substandard manufacturing processes in generic valsartan manufactured in China and distributed in the US, followed by Trump’s increased rules around investments in China or by China-based entities in the US, followed by … CRISPR babies.

CRISPR babies almost sealed the deal for not moving forward with this February topic, but the other editors talked me off the ledge and here we are with a well-rounded issue on the state of biopharma in China. And what I’ve learned interviewing China’s pharma industry watchers and participants, is what looks like a negative setback is actually part and parcel for the country as it grows its innovative medicines and increases quality standards in a very remarkable upward curve.

One of those industry watchers, Bill Trombetta, PhD, professor of healthcare strategy and marketing at St. Joseph’s University’s Haub School of Business in Philadelphia, last visited China in 2013 with a group of graduate students. The first such tour was in 2002 to learn and observe in Hong Kong at the time of the transition from UK affiliation to China’s authority and control. The 2013 grad study tour in Beijing included visits to a number of stakeholders, including a “small mom and pop drug” manufacturer, Bayer and Novo Nordisk, a CRO, a medical school, and hospital.

With every visit, Trombetta said China changed immensely. From developing large industrial parks—what used to be rural areas to developed and easily accessible suburbs, as well as advances in the drug channel, Trombetta continues to watch the country evolve its pharmaceutical capacity. My discussions with him frame the article on page 18. Similar observations are borne out in our reporting. Strikingly, are the advances in the Chinese regulatory process for drug development and manufacturing. Though the bad apples in manufacturing are still clearly a concern, the court of public opinion is pressuring the government to act not just through prosecutorial means, but through a regulatory process that should weed out the bad actors and improve the overall quality of the supply chain.

IP concerns have been reduced, mostly through stronger legal contracts and understanding. If you check out these videos (bit.ly/2WuE42s) with our Senior Editor Michelle Maskaly at a ChinaBio event during JPM in early January, you’ll see that these executives don’t view IP as the barrier it once was.

According to reporting by our European Editor Julian Upton on page 15, Christian Hogg, CEO of Hong Kong-based biopharma company Chi-Med, observed that protectionism has melted away over the last 10 years, as the country has listened to multinational companies.

In addition to China’s government changes and growing middle-class, a major influencer is the educated, skilled, and entrepreneurial individuals who have returned from their ex-China experiences with the desire to improve and invest in the legitimacy of China’s science. Quality in development, IP, manufacturing, processes is very important to them because they truly want to be viewed as an equal player on the world biopharma stage.

But even as we were putting our coverage together, yet another scandal occurred—the reports that approximately 145 children had received an expired polio vaccine in the Jinhu province. Not necessarily a manufacturing problem, but it marks the fifth vaccine-related issue in the country in the past seven years. Enough for parents and citizens to gather publicly and voice concerns to their government. Enough of an incident for the media here and there to cover it and wonder if China can get its policies in order. In general, another knock against the overall ability of the country to take it to the next level.

In comparison, the FDA regularly investigates and fines entities and individuals for manufacturing problems, GCP violations, labeling and advertising inconsistencies, and government-influenced issues outside of regulatory, such as pricing. These also make the headlines in the US and lead to an overall picture painted for the public and for policy development. It’s not just in China, governments all over struggle with their own cultural norms, practices, and public pressures.

I’m still a bit wary about my career obstacles for 2019, but my horoscope also said that if I persevere, I will overcome these challenges. So no smooth sailing for me this year, but also for biopharma in China. What looks like two steps forward, takes one step back. But patiently persevering, even with one step back, or climbing over another high step, eventually you are still moving forward.
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Congressional leaders are opening investigations and calling industry leaders to testify at hearings on drug costs and pricing strategies. Legislative proposals are emerging to permit greater drug importing, require price disclosure in TV commercials, limit pay-for-delay deals, and more. The Trump administration is devising new strategies to limit Medicare outlays for medicines. And hospitals are continuing to push for attractive 340b discounts.

And there’s more to come. Both the Trump administration and Congressional leaders agree on the importance of making prescription drugs more affordable and accessible, and all sides are lining up proposals to grab the spotlight. There is strong interest in measures that tie the prices of U.S. prescription drugs to median prices in other developed countries, and to allow Medicare to negotiate drug prices.

In the House, Oversight and Reform Committee chair Elijah Cummings (D-Md) has requested pricing and cost information from a dozen leading biopharma companies as part of a broad investigation he has opened into strategies to reduce prescription drug prices. Both Cummings and Senate Finance Committee chair Chuck Grassley (R-Iowa) scheduled hearings in late January on a range of initiatives to lower costs for patients, as Grassley looks for support from Senate Republicans and Democrats for strategies to curb high drug prices.

A lead proposal is to make it easier for Americans to purchase less costly, but supposedly safe, drugs from Canada. Grassley backs a bill that permits such transactions from “certain approved pharmacies” in Canada, despite long-held concerns by FDA officials and others that there’s no way to assure the provenance and legitimacy of such products. Some Democrats have gone further, permitting drug imports from a range of countries. Meanwhile, FDA is responding to the clamor for relief by exploring strategies to safely import drugs in situations where there are dramatic price increases or serious shortages.

Another high-profile initiative is to require price disclosures in drug TV commercials, which was proposed last year by the White House and is popular on Capitol Hill. Researchers are busy examining whether such information would actually help consumers make better treatment choices, and industry is pressing for linking price disclosures to websites. Senate Democrats also are looking to revoke the federal tax deduction for prescription drug advertising, a perennial tactic that has fallen by the wayside in the past, but now may gain traction.

Examining competition
Brand pharma companies also face continued pressure from generic drugmakers for legislation to limit apparent anti-competitive behavior. A main initiative aims to reduce barriers to obtaining needed drug supplies for conducting studies required to demonstrate that a follow-on product is bioequivalent to the brand. FDA backs such measures as a way to enhance competition in certain therapeutic areas, particularly for complex products and dosage forms.

The role of drug rebates, discounts, and co-pay cards are on the table, as Sen. Susan Collins (R-Maine), who chairs the Senate Special Committee on Aging, focuses on links between rebates and prices. Collins is examining claims that pharma companies raise list prices in order to offset deep discounts demanded by payers and has asked the administration for data on the role of rebates, discounts, and coverage decisions in shaping what consumers pay and how insurers benefit from these arrangements.

Policymakers also are examining rising prices for insulin, building on press reports about individuals with diabetes struggling to afford critical injections. While many diabetes therapies are covered routinely by health insurance plans, people without adequate coverage have been hit hard. Certain long-established diabetes drugs have doubled in price in the last five years, according to recent analyses, despite ample supplies.

The attack on high drug costs has been a boon for the Institute for Clinical and Economic Review (ICER). It recently announced that it would expand from assessing the cost-effectiveness of new drug launch prices to also evaluate whether price increases of certain marketed therapies are justified by additional clinical evidence of added benefits.
Case study outlines the potential benefits for a life sciences organization in adopting a mindfulness approach across its leadership groups

By Janet Matts, Raymond Sanchez, and Timothy Peters-Strickland

The benefits of mindfulness have been studied extensively, both in the lab and in the field. In particular, the benefits of applying its principles and practices in the business world—from fostering thoughtful leadership to enhancing organizational productivity and strategic decisions—have been a robust area of exploration over the last decade.

Large companies, including Aetna, Intel, McKinsey, Genentech, and General Mills, among many others, have collaborated with mindfulness leaders like Dr. Jon Kabat-Zinn to implement mindfulness programs in the workplace. In many ways, the tech industry has been a trailblazer: Chade-Meng Tan developed the now-famous Search Inside Yourself program while at Google—a program that has since been implemented by numerous companies across the globe. The sports world has also embraced mindfulness, in the form of meditation: Michael Jordan, Shaquille O’Neal, and Kobe Bryant—all titans of the NBA—have each consulted sports psychologist and mindful meditation teacher George Mumford to improve their performance.

Could a mindfulness program have a measurable impact in pharma?

In 2014, Otsuka Pharmaceutical Development & Commercialization (OPDC), having just had its first successful filing for Abilify Maintena, was looking for ways to help the organization manage
an increased portfolio demand with ambitious timelines. Dr. Raymond Sanchez, senior VP of global clinical development, became interested in mindfulness as a potential way to enhance performance, increase creativity, maintain objectivity in decision-making and conflict management, and support “people development” within the company.

“We wanted to continue the motivated passion of those in the field to develop novel therapeutics to address unmet medical needs,” Sanchez explained. “This development would enhance company values and allow personal and psychological health benefits for employees living in our global environment of innovation, change, and drug development challenges. We spend lots of money on the development of new drugs—clinical trials and research—but need to spend more time and effort on developing the leaders and teams who support these endeavors.”

Consequently, the question at OPDC became: “What if we focused, not only on the ‘doing’ of leadership, but also on the ‘being’ of it?” What makes a leader successful? That question of “being” successful leaders became the heart of an in-house mindfulness study initiated by Janet Matts in Otsuka’s New Jersey offices.

The initial group consisted of eight senior medical leaders—MD and PhD researchers with experience, flexibility, and a desire to grow their leadership capabilities across the organization—and an external consultant. The vision of the group was to “create a world-class clinical development organization that provides leadership and innovative approaches to the development and delivery of novel therapies on time and on budget, to improve human health worldwide.” They decided to approach this goal using mindfulness in two complementary ways (both in tandem).

**Monthly mindfulness sessions.** These included guided meditations, stretches/yoga postures, and a healthy community “mindful lunch.” This was a voluntary (not mandatory) practice.

**Monthly one-on-one executive coaching.** This focused on leadership development and creating an individual, actionable mindfulness practice. The benefits of this strategy, which was mandatory, included greater integration of mindfulness into the personal/professional development of each participant.

The monthly mindfulness sessions provided a “thoughtful space” to quiet participants’ minds and enhance their individual behaviors. It also encouraged them to frequently consider the type of leader they were. At the same time, the individualized executive coaching sessions provided an opportunity to actualize a daily mindfulness practice within a busy schedule.

Some participants were eager to partake while others had a “wait-and-see” approach and were convinced to join the practice after witnessing the success of the initial group over time. As such, the sessions increased in enrollment over several months.

### Key success factors
The hope to develop successful leaders who would influence the organization in positive ways drove development of these ongoing mindfulness initiatives. A summary of critical success factors for implementing a mindfulness focus is provided in Figure 1.

Strong leaders exhibit certain fundamental characteristics: they lead by example, focus on priorities, and consider people development as critical to the organization. More specifically, these qualities include:

- Senior, visible role that engages leadership development within the organization.
- Viewing oneself as a change agent.
- Maximizing creativity.
- Paying attention to practicality as a person.
- Being energetic and forward-thinking.
- Caring about the development
The Mental Edge

Benefits from a mindfulness approach include but are not limited to:

- Personal and professional growth and development.
- Improved overall focus; attainment of greater peace of mind.
- Improved objectivity and productivity.
- Development of a “laser focus” for projects and deliverables.
- Promotion of healthier team environments due to healthier team leaders.
- Encouragement on a better work-life balance.
- Improved work satisfaction.
- Facilitation of greater self-enhancement.

of people to ensure a well-rounded approach for maximizing successful physical, mental, and spiritual outcomes.

It was also important that the mindfulness practice grow organically, initially by early adopters and then spreading to others in the organization after witnessing its success. This “do a little, learn a lot” attitude allows a novel program to spread on its own throughout the company. Early adopters are seen as curious and pioneering, which piques curiosity in others and encourages their participation over time.

Focusing on techniques that support stress reduction is another important priority in our global environment of innovation, change, and drug development challenges.

Measuring success

For the initiative’s success, it was important to link these practices to meeting the goals inherent to our business, specifically, the leading of development teams, achievement of innovation goals, and enhancement of key aspects of the company culture.

The impact of the ongoing mindfulness practices—on both personal measures as well as business metrics—were documented over time. Some especially telling testimonials from participants were:

- “By taking the time to create mindful outcomes and visualize success, my meetings are much more successful.”
- “Conflicts are easier to deal with when I am aware of my emotions and can mindfully pay attention to their outcomes.”
- “Hmm…that is a ‘trigger’ for me, so do I choose to respond in the same way that I always have? I can change that choice!”
- “When I pay attention for ‘being’ rather than ‘doing,’ I have much greater emotional control.”
- “When I am ‘in the now,’ my creative juices flow easier.”
- “If I stay mindful, I have less anxiety, and more focus and creativity.”
- “My creativity is heightened, and my objectivity is maintained when making decisions.”
- “I can be a better leader, and a better dad at home when I am ‘tuned into’ being present for whatever place I am in.”
- “I understand that as an introvert, my initial response is sometimes not to respond. Being more mindful has taught me that the leadership role that I play requires me to ‘step up,’ even if my preference is to hold back. This has allowed my leadership insights to be heightened.”

On the business side of the spectrum, results—outlined ahead—show the evolution of OPDC’s central nervous system (CNS) development programs. We found substantial increases in professional achievements for those involved in the mindfulness practices. The Abilify team worked together to gain approval for five new indications, in addition to approval for the first-ever digital medicine new drug application (NDA). The Rexulti team completed 56 clinical trials with approximately 12,000 patients, resulting in an NDA and approval for dual indications: schizophrenia and major depressive disorder.

The ROI for mindfulness practices provided strong evidence of success. The mindfulness initiative group has had prolific results with a handful of CNS leaders. The group, overall, has had low turnover, a highly productive attitude, and unparalleled results in the organization. Late in 2015, the group was expanded by five people to include all clinical development leaders, not just CNS. Additional results include the recent approval of Samsca.

As interest in the mindfulness program has continued to grow, Matts suggested adding a third element—education on mindfulness research—at the team’s ongoing off-site leadership development meetings, to reinforce the principles and efficacy of mindfulness with research validation.

As a result, at meetings in March 2017 and April 2018, Dr. Ellen Slawsby, from Massachus
setts General Hospital, shared her research findings on the benefits of mindfulness and its applications, from chronic pain, to overall health and wellness (i.e., stress reduction and sleep, diet and exercise improvements). In addition, the work of Michael Carroll, Jon Kabat-Zinn, and others were introduced in the monthly practices, to keep those sessions diverse by highlighting new ways to practice mindfulness.

A model for others?
Applying a multi-faceted mindfulness practice in a disciplined and thoughtful way can bring significant results, including a more integrated work-life balance for those in a demanding clinical development environment (see sidebar on facing page). A part of this process since its initial inception, Tim Peters-Strickland, VP, CNS drug development and digital medicine, noted, “I have experienced many important benefits; not only professionally, but personally as well. How many other practices can give you an ongoing opportunity to stay focused and make critical decisions in the busy and demanding world of drug development?”

It is our hope that sharing this in-the-field study of mindfulness practices in a pharmaceutical company will be a pathway for others in the drug development arena to become aware of the benefits and effectiveness of such practices. Further, we hope that other companies will implement practices like those outlined here to promote the growth of clinical development leaders and enhance their productivity and success.

References
A Leading Man’s Next Act

Applying lessons gained along a prolific path in the pharma industry, including 17 years leading China operations at multinational big pharmas, Xiaobin Wu believes his jump to biotech as GM of China and president of BeiGene will deliver his most lasting career impact.

By Lisa Henderson

Dr. Xiaobin Wu has been general manager of China and president of BeiGene, Ltd. since the end of April 2018. With more than 25 years in the industry, like many executives who make the move to biotech, Wu has deep roots in traditional pharma. Prior to his most recent appointment, he was the country manager of Pfizer China and the regional president of Pfizer Essential Health for Greater China from October 2009 to last April; president and managing director of Wyeth China and Hong Kong from August 2004 to October 2009; and served in increasing roles of responsibility with Bayer, where Wu started his career in 1992 in sales and marketing in Germany. He received advanced degrees—a masters in molecular biology and PhD in biochemistry and pharmacology—at the University of Konstanz in Germany.

“When I came to Germany in the early ’80s, it was very rare for professors to see a Chinese student. I remember very clearly the first time one of them met me, he almost fell from his chair,” explains Wu. The young scientist began to understand that China itself was a mystery to most people in the West, but it didn’t hold him back from his studies. And while Wu successfully progressed along the science track, he admits that it wasn’t his true calling. “I worked very hard. I was published, but I looked at my colleagues in the laboratory and they were much better than I was,” says Wu. That was when he made the decision to alter his career pathway and take his scientific education directly to Bayer.

There, too, Wu believes he was the only Chinese national working in an area of Germany near Switzerland. “There were not many Chinese people in that region,” he says. Wu applied his PhD expertise directly to his role with physicians. “I could speak their language and articulate the science very well.
to them.” Within three years, Wu was promoted into Bayer’s central marketing and in charge of multiple brands.

In 1996, the big pharma asked Wu to lead its co-founded joint initiative in China as marketing head, where, subsequently, he became general manager for Bayer Healthcare in China. “Bayer has been there from the very beginning of the modern China pharmaceutical industry,” says Wu. “It is a very significant company in the country.” (see bit.ly/2HFVPbZ)

In 2003, Wu was approached by a smaller American drugmaker, Wyeth, to become its GM in China. The company assured him he would be a perfect fit, but Wu was not easily swayed. “Although they told me I would be working with nutrition and could learn OTC (over-the-counter), it was a smaller company. Why would I want to move? I was not convinced,” he says.

The courting period lasted a year, and Wu was swayed when a friend told him that although he had a proven track record with European companies, he didn’t have experience with a US one. “If you want to have success in industry, you have to work for a US company,” Wu recalls of his friend’s advice. “I realized it was the missing piece of the puzzle. I wanted that different experience working with a US company.”

Wu took over Wyeth China and was headquartered in Shanghai for five years. He looks back at this time period as a turnaround situation. Wyeth, he says, was not in good shape in China, but the company grew its business there from $70 million to $800 million during that timeframe.

“It was all in infant formula. But I did learn a lot,” says Wu. In 2009, Pfizer acquired Wyeth, and as they merged the companies, Pfizer named Wu GM of the combined group in China. “The Pfizer leadership was very focused and challenged with bringing a good pharmaceutical company to China and to become an even better company and moving quite fast to do so,” says Wu.

Programs transitioned to Wu and his colleagues included large-scale ones such as the nationwide cardiovascular disease management initiative, “Bending the Curve,” which educated patients around CV incidence.

While at Pfizer, Wu was also able to grow the business in China from less than $1 billion to over $4 billion in 2017. “We had tremendous growth and I had tremendous experience,” says Wu, who was promoted into Bayer’s central marketing and in charge of multiple brands. As I look at my career to date, I know this will be where I most build my legacy.”

What experiences has Wu brought to his new position with BeiGene? He views his time with Bayer in China as kind of a start-up environment. While he was versed in the processes and standards of the company in Germany, he had to transfer it all and develop it to the healthcare unit in China. As noted, Wu classifies Wyeth as a turnaround situation, and learning new markets. Of Pfizer, he says, “I learned so much and the company has contributed so much to China and the Chinese pharmaceutical industry. They connected China to the Western world and brought the standard-of-care concept to Chinese physicians. They have increased the healthcare education, skills, and competency to bring China closer to the standards of the rest of the world.”

How does Wu view BeiGene’s current path? “I see some chal-
lenges, but that is what I was looking for, otherwise life gets too boring,” he says with a laugh. “Working for big pharma, it has its processes and systems and it’s very structured with excellent support from all your regions. In coming to startup biotech, there are a lot of good and talented people, just like in the multinational companies, but they don’t have as much of the established systems. Some of that is good, and some of that can be challenging.”

“As I look at my career to date, I know this will be where I most build my legacy.”

For example, Wu believes, some things can be overlooked in communication with smaller teams—not intentionally but because someone possibly forgot, or might not even know the right content or question to ask. “I’ve instituted a more formal system for the different groups to get together to discuss and talk through the issues,” he says. And, similar to many cases when executives jump from pharma to biotech, there is the “multi-hat” phenomenon. “For the large multinationals, you are very focused at different functions. Here, it is new, and you have to do a bit of everything,” explains Wu. “I deal more directly with medical and R&D. I’m much closer to the science at BeiGene and I’m very excited about that.”

Building teams over the course of his career, Wu first looks to see if potential hires have the right ethics and values. “These characteristics are particularly important, as I believe that it’s critical that you show leadership by example,” he says. “There are no shortcuts in our industry, so someone with the right values will eventually go higher in their career and be the type of person that a team will want to follow, learn from, and work to their very best every day. I value a person with the highest ethics over anything else.”

2019 may go down as a pivotal year for BeiGene. Last month, the Chinese biotech was granted FDA breakthrough therapy designation for its investigational Bruton’s tyrosine kinase (BTK) inhibitor, zanubrutinib, for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Zanubrutinib, being developed in a clinical program that includes seven Phase III trials, is the first drug candidate discovered in China to gain FDA breakthrough therapy status.

BeiGene is anticipating that two new drug applications filed in 2018 to the Chinese regulatory authority, the National Medicinal Products Administration, will be approved this year. They are for zanubrutinib for patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), and for tiselizumab, an anti-PD-1 antibody.

And while BeiGene already markets Abraxane (nanoparticle albumin–bound paclitaxel), Revlimid (lenalidomide), and Vidaza (azacitidine) in China under a license from Celgene (whose contract stays in place through the Bristol-Myers Squibb buyout), the 2019 launches would represent the first time BeiGene’s scientists and researchers have taken a compound to commercialization. “There is a lot of coordination around launch readiness,” acknowledges Wu.

Product launch and market access in China is a much different model than in Europe or the US. There is reimbursement on a provincial level and hospital listings have improved, but, by and large, it is an out-of-pocket payment by the patient. Wu says bringing an approved product to the patient has its hurdles.

Away from the day-to-day challenges, Wu continues to look at the biotech and pharma landscape in China as one of promise. He sees the movement of talent among executives and the workforce shifting to biotech, and, going forward, bringing fresh ideas to both sides of industry.
New Roads to China

How the nation’s rapidly changing regulatory climate is creating a new landscape for pharmaceutical service providers

By Julian Upton

One marker of the pace of change currently under way in China was highlighted at the FT’s annual Pharma and Biotech Conference in London in November. To the polling question, “When will China be a significant influencer of innovation?” half the audience answered 2025. This prediction might be surprising to those who have taken their eye off the ball, but the country’s intensive commitment in the last few years to a program of regulatory advancement is swiftly changing the Chinese pharma and healthcare market. So much so, one of the FT conference speakers, Christian Hogg, CEO of Hong Kong-headquartered biopharma company Chi-Med, proclaimed that 2025 is a “conservative” estimate for China’s breakthrough as the world’s pharma powerhouse.

Navigating the new terrain

The changes in China have resulted in “an extremely dynamic landscape for companies looking to enter the market,” says Dr. Chang Lee, vice president of consulting for Parlexel in China. In October, the CRO announced the launch of a new China Advisory Service to help global biopharma companies “navigate all aspects of the country’s drug development process.”

Lee told Pharm Exec: “Four years ago, clinical trial approval from the Chinese FDA (now the National Medicinal Products Administration [NMPA]), took about 10 months. Now, by law, it is just 60 working days. Second, there’s a huge market from the Chinese reforming of the drug formulary coverage. It is now much easier for insurance companies to cover a drug, to get drug approval, and to get a drug on the national formulary. This has attracted pharma companies back to China.”

Roel de Nobel, vice president, global operations, clinical supply services at Catalent Pharma Solutions—which announced its plans in November to invest $2.5 million in a new, second clinical supply facility in Shanghai—told Pharm Exec that, as a result of NMPA significantly shortening the lead time associated with granting a new clinical trial approval, “we have seen a significantly increased interest from multinational pharma in bringing their drug development activities into China.” He adds: “We expect this trend to continue, given China’s large and easily accessible patient pool, and supportive healthcare infrastructure.”

As Lee noted, however, “the ability to quickly understand and adapt is critical to succeeding in this rapidly changing environment.” While the reforms have made the regulatory environment in China more accessible to pharma companies, barriers to entry still remain. These include government-mandated price controls in public medical insurance...
programs, complex price negotiation processes at national and province levels, complex distribution channels, infrequently updated formularies, and an absence of GMP-compliant manufacturing testing sites and GCP-compliant clinical sites.

“In just a short time, China has grown from being an emerging market for companies looking to develop drugs to the second-largest biopharmaceutical market in the world,” says Paul Bridges, Parexel’s corporate vice president and worldwide head of consulting. “While many are aware of the opportunity that exists in the market, the challenges and hurdles to entry are generally not well understood.”

For example, Bridges told Pharm Exec, “there are so many changes to regulations that the implementation of those changes will take time. It is too early to know how the newly formed NMPA will approve new drugs for national insurance coverage consistently. Also, there are limited local key opinion leaders to advise on China medical practice patterns and evaluate unmet medical needs.” As more R&D companies look to penetrate this market, he says, the need for advisory services will continue to grow.

**CRO plus**

A 2017 Research and Markets report predicted that the CRO industry in China—driven by the favorable policies, more spending on R&D, and an increase in the number of new drugs approved—will reach an estimated RMB116.5 billion ($17.1 billion) by 2021, with Chinese pharma R&D spending of up to $29.2 billion driving the development of the CRO industry from supply side. Currently, the top 10 global CRO companies, including Parexel, IQVIA, Covance, Syneos Health, and Charles River, hold a combined 45% market share in China, but the pace of regulatory change in the country has intensified demand for talent in this area. Lee told BioSpectrum Asia in October that “the biggest challenge for CROs in China currently is the lack of an adequate clinical research infrastructure, specifically; limited research sites; lack of qualified principal investigators and research staff; and inefficient institutional review board (IRB)/ethics committee (EC) processes, among other challenges.”

In December, Parexel struck a new collaboration with Eli Lilly to launch a clinical research learning and development program in China to “bring high-value training opportunities to China’s clinical trial sites and investigators, enhancing the execution of local clinical trials.”

There is growing competition for western companies, however, from the domestic CRO space, with companies such as WuXi AppTec, Pharmaron, Shanghai Medicilon, Hangzhou Tigrmed Consulting, Joinn Laboratories, and Quantum Hi-Tech Biological reportedly pushing the development of the clinical outsourcing industry in China. In 2017, Quantum Hi-Tech acquired ChemPartner, one of China’s biggest chemistry service providers, and state-owned Xinjiang Baihuacun entered the R&D market with a $270 million investment in Huawei Medical.

As China continues to attract overseas pharma to expand their territories and capabilities in new drug R&D, “the leading Chinese CROs will be at forefront… gradually becoming their priority suppliers and important strategic partners,” wrote Jin Zhang in an October 2017 entry on her thefierceconsultant.com blog. While the preclinical CRO market is relatively small, things are changing, she added. “In light of the Chinese government’s support of drug innovation and the convergence between China and global medication standards, an increasing number of domestic pharma companies are slated to devote more resources and apply more capital to innovative medication development.”

Lee sees the traditional, clinical trial-focused CRO model developing into a “CRO plus” model in China. “For example, this might include CRO plus marketing data; CRO plus clinical lab; CRO plus contract manufacturing organization (CMO); CRO plus technology (e.g., AI, big data).”

On this front, the Shanghai-based giant WuXi AppTec (which accounted for 9.5% of the Chinese CRO market in 2016) has embarked on a program of national (and international) expansion, which, in 2017, saw its drug development business services merge with its active pharmaceutical ingredient (API) production business, STA Pharmaceutical. The firm announced that it would be building a new site in Changzhou, China, featuring nine large manufacturing facilities. According to published reports, by the middle of last year, WuXi had reached a third of this target, with three commercial-scale facilities completed, making the company a sizable CMO as well.

**Opening up to CMOs & CDMOs**

While, for many people, “outsourcing to China means WuXi” (as PharmaBlock Sciences CEO
Haijun Dong was quoted as saying in Chemical & Engineering News last year, the need for contract manufacturing services in China is growing, with more biosimilars and innovative drugs entering the clinical pipeline but with most early-stage biologics developers in China lacking manufacturing facilities.

Vicky Qing Xia and Leo Cai Yang of BioPlan Associates wrote in 2018 in Contract Pharma that, “China is demonstrating clear investment interest in participating in global markets for both innovative biologics and biosimilars produced at GMP quality levels.” They noted that before 2016, pharma contract manufacturing for domestic drugs “essentially did not exist in China,” because of a regulatory framework that precluded third-party/CMO manufacturing for either clinical trials or commercial production. In 2016, however, China established the pilot Market Authorization Holder (MAH) program, under which holders of a Chinese FDA biologics approval number had the option to manufacture the drugs or use a CMO. “It is widely expected that the regulatory hurdles for contract manufacturing of drugs in China will shortly be removed,” Qing Xia and Cai Yang added. (It is now believed that the MAH will not become law before 2020.)

BioPlan Associates’ 14th Annual Report and Survey of Biopharmaceutical Manufacturing, which asked global respondents to evaluate their facility’s current plans for future international capacity expansion, revealed in April 2017 that China had for the first time beaten Germany and Singapore to fourth place as a potential outsourcing destination (the US remained the top destination). Qing Xia and Cai Yang concluded in Contract Pharma that an expected rise in quality standards for manufacturing in China is “also likely to bring good news to vendors of new bioprocessing technologies, products, and services.”

In 2017, Boehringer Ingelheim was the first multinational company in China to set up a CMO project in line with global standards. With an eye on increased future demand, its China biopharmaceuticals site in Pudong, Shanghai, reportedly has a capacity of four 2000 L single-use bioreactors. Boehringer Ingelheim has been active in lobbying for MAH reform, and in January 2018, the company announced that BeiGene’s solid tumor treatment, tislelizumab, would be the first monoclonal antibody (mAb) to be produced at its Shanghai site, and the first to be made by a foreign CMO in China. Commenting at the time to BioPharma-Reporter.com, Diane Lam, marketing manager for the Swedish–Chinese contract manufacturer Wuxi Griffin, said that with “less than 10 Chinese CMOs complying to western GMP,” it was likely that more international CMOs would establish a presence in China.

de Nobel expects the growth of service providers in China, both international and domestic, to continue the foreseeable future. He told Pharm Exec, “There is an opportunity for large global contract development and manufacturing organizations (CDMOs) to help prepare local Chinese pharma companies to expand beyond China in understanding global best practices, quality standards, and other regulatory requirements that they may need to follow outside of the country.”

He added: “The challenge is to be a global company that also establishes truly local operations that thoroughly understand the local language, regulatory, business, and cultural environment and the importance of building relationships within the country. To this end, localization of services is part of Catalent’s strategic focus for China and the APAC region.”

**Risks and rewards**

At 6%, China’s healthcare spending as a portion of GDP still lags behind the US (17%) and Europe (10%). But, as Chris Lo pointed out in Pharma Technology Focus in November, this indicates that “the market is still primed for further expansion.” He added that, with the healthcare market expected to reach $2 trillion in value by 2030 (the country’s over-65 population will increase from 90.6 million people in 2017 to 143 million in 2027) and the official acknowledgement that foreign companies have a large role to play in meeting the country’s health objectives, “there’s never been a better time for the pharma industry to invest in China.”

While risks remain there, Mark Mallon, AstraZeneca’s EVP of global product and portfolio strategy, medical, and corporate affairs, told the FT Pharma and Biotech Conference in November, “the opportunity to make a difference to vast numbers of people outweigh those risks.”

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China: A Change in Attitude

Innovation forces upgrades in regulatory, quality, and standards to ensure the country is competing on a global level

By Lisa Henderson

The pharmaceutical industry in China is definitely not a new thing, but for the past three to five years, there’s a definite twist on the old thing. One that is more akin to western countries in regard to innovative growth, regulatory, and adherence to standards. There are a number of separate events that, taken together, have inspired this pivot and new attitude.

Last year, management consulting firm L.E.K. Consulting issued a report called “Heading East: Biopharma International Expansion to China and Asia” (bit.ly/2B2FzMn). According to the report, in 2017, the top four countries for global pharma spending were the US at $467 billion; China, $123 billion; Japan, $85 billion; and Germany, $45 billion. L.E.K. also projected those numbers to grow, respectively, by 2022 to $600 billion; $160 billion; $87 billion; and $56 billion.

But those are the numbers. Here are the reasons.

Innovation

Helen Chen, Greater China managing partner and head of China and Asia life sciences for L.E.K., told Pharm Exec that China’s desire to increase innovation is not solely in the pharma purview. It resembles Germany’s Industrial 4.0 framework, with a focus on robotics, AI, and medical devices as well. “As an industrial policy, the country is trying to upgrade itself to have higher value,” says Chen. She believes the innovative leaders in industry are the ones lobbying and facilitating this change in China similar to how Europe and the US does things.

That sentiment is evident from the experience and ideas of one Chinese biotech CEO and chief scientific officer, Xiaoqiang Yan of Generon Biomed, a biotech subsidiary of Yifan. Yan received his PhD in molecular and cell biology at the University of Toronto. He then worked for Amgen as a research scientist from 1993 to 2002, before he returned to China and co-founded Generon in 2004. During his time in the US, Yan observed that the big biotechs—Amgen, Genentech, and Biogen—built their own manufacturing plants. “In my experience, they all did that because of the complexity of the product they were manufacturing and they needed that process control,” he says. “Therefore, they developed their own manufacturing science, because they understand the biology and the biophysical properties of their product.”

Yan, too, believes that complex therapies, including his company’s own CD3 bispecific antibody platform for immunoncology, targeting and its recombinant human cytokine dimer platform for receptor activation, require improved and robust manufacturing processes as keys to success. Therefore, Generon Biomed is building its own cGMP biological manufacturing plant, which will be FDA/EMA/NMPA-compliant. He told Pharm Exec, “China and the US used to have huge gaps in GMP (good manufacturing practice). We want to have that FDA approval, because we want to guarantee the high quality of the product and the standards. Those are critical factors for patients as well.”

Manufacturing

There has been a long history of quality issues in China that get media attention and seem to set public perception back around drug and biologics in the country. As recently as mid-January, the government is investigating how 145 expired polio vaccine vials were given to children. While not necessarily a manufacturing issue, it follows the July 2018 injection of Chinese children with faulty DTaP vaccine, resulting in a $1.3 billion fine against the manufacturer, Changchun Changsheng Biotechnology Co., Ltd.

Largely, quality issues can be traced to the country’s history of manufacturing generic drugs, a landscape that featured 6,000 manufacturers in 2000. According to Chen, China has gone through multiple stages of upgrades to its GMP requirements, and with each stage requiring a higher level of rigor, manufacturers, mostly smaller ones, have closed shop rather than spend the money to upgrade their processes. That weeding out has brought the number of generic manufacturers to 4,000.
The last regulatory round instituted a bioequivalence requirement. Chen says, “Generics used to not have a bioequivalent requirement to the originator. The government instituted a rolling requirement for the first 289 essential drugs in the oral class, which needed to prove bioequivalence to the originator in order to stay in the system.” As part of the process, the government will discontinue all other generic brands not meeting bioequivalence once three products per molecule have received GQCE, or generic quality consistency evaluation.

Again, this process is applying higher rigor and stringency to generic products in China, but, clearly, following upgraded GMP impacts the rest of drug manufacturing. It speaks to the desire to have quality drugs available for patients in the country and how companies like Generon see that high-quality manufacturing can inspire consumer trust for a drug or biologic.

Venture capital and funding
A new plan unveiled in December 2017 aimed to bring more IPOs to the Hong Kong Stock Exchange. Under the new rules, biotech companies in particular need not have a revenue requirement, or a revenue track record. However, they must have a market valuation of at least $1.5 billion (HK) at the time of listing, one “sophisticated” pre-IPO investor, and a product that has passed a Phase I clinical trial for safety and has regulatory approval to begin the efficacy portion in Phase II. This clearly is a huge boon to biotech in China, which the government has said will grow to 4% of the country’s GDP by 2020. Meanwhile, the Trump administration’s changes to the Committee on Foreign Investment in the United States (CFIUS) affect investing in China biotech, as well as China investing in US-based biotechs (see related story on page 22).

Regulatory
The regulatory environment in China was not always as conducive to innovation and China’s drug and medical device regulatory agency has evolved since 2008, first from the SFDA to the CFDA, and then, since 2018, the NMPA, or National Medical Products Administration. In each instance with the CFDA and NMPA, the goal has been for the Chinese regulatory process to mimic and work in harmonization with the other large global agencies.

Specifically, since 2017, the NMPA has made some notable changes that have impacted drug development in China. For one, the Clinical Trial Application formerly required that three batches of drug be available for testing, which is “very costly for a novel drug, and not entirely realistic,” says Chen. That requirement has been removed.

The next change is allowing the submission of clinical trial data conducted globally, not just on Chinese patients. In July, the NMPA published the “Technical Guidelines for Acceptance of Overseas Drug Clinical Trial Data,” outlining its new direction. “These are clear examples of the regulatory agency trying to align its systems with other markets,” says Chen. “It makes it easier for ex-China companies to do business in the country, but it also helps Chinese companies to adapt their processes and be more aligned with other markets when doing submissions.”

Another change is the faster approval pathways, similar to the FDA’s priority review, breakthrough therapy, accelerated approval, and fast track. According to Chen, an expedited review process has been in existence since 2009; however, it became more actively defined and publicized in 2016.

China and the US used to have huge gaps in GMP. We want to have that FDA approval, because we want to guarantee the high quality of the product.”

Healthcare
While the discussed factors focus more around innovation and reasons for an expanding pharmaceutical market, the facts around China’s healthcare system have clear differences that pharma and biotech companies will need to understand. As noted in L.E.K.’s report, there are a number of ways to tackle the Chinese pharma market. One is partnering with a company in China because of its cultural fit, market access understanding, and experience in the region.

Here’s a well-known fact about China—it has a lot of people, 1.4 billion. For comparison sake, the US has a population of 325.7 million.
But the recent past has seen the number of people living China’s urban areas rising steadily; as of 2015, this segment represented 55.8% of the nation’s population, vs. 44.2% in rural. China is also experiencing an increasing wage gap, with a growing income disparity that resembles that of the US. China has a 46.5 Gini coefficient, which is a global benchmark for the measure of income disparity, while the US has a 47 Gini coefficient. The income disparity question is something that China, as well as the US, will need to address at some point; but what it does speak to for biopharma purposes is a growing middle-class with disposable income in China. The nation’s healthcare is largely fee-for-service, a consideration for product launch, and medication maintenance.

In 2017, healthcare as a proportion of GDP in China was only 6.36%, compared to 18% in the US, the highest rate globally. Japan’s and Germany’s are 11% and 11.2%, respectively. Many believe that more investment in healthcare is needed, which would be costly, but it doesn’t need to equal the levels of the US.

While healthcare insurance is a public system with mix of private (employer-based) as well as public contributions, as noted, services and drugs are often paid out-of-pocket. The government does procure essential drugs and most are dispensed through hospitals. A new pilot procurement system has been recently initiated in China, with the government reaching out to the manufacturers of 31 essential drugs asking for their best price for a guaranteed number of sales. According to industry watcher Dr. Bill Trombetta, professor of healthcare strategy and marketing at St. Joseph’s University Haub School of Business, who has taken graduate students to China to visit with top pharma, CROs, hospitals, and wholesalers for first-hand experience (see page 3), some manufacturers cut their prices upwards of 90%, though the average was closer to 46%. To Trombetta, the math makes sense. “If there are 140 million people in China with diabetes, which is half of the US population, you cut the drug’s price by 70% but still reach all of those people, that is still a significant amount of money,” he says. However, Chen believes the pilot bears watching, as there has been some backpedaling by the Chinese on how many patients they are guaranteeing access to on the contracts.

Another difference is that the “trusted” physician relationship that most western countries recognize is not a feature of China. In fact, that relationship ranges from distrustful to downright adversarial. In China, as of 2014, there were 1.7 doctors per 1,000 people. As a comparison, the US has 2.6 doctors per 1,000 people and Germany 3.7 per 1,000. “It is very difficult to see a doctor in China,” says Trombetta. And when patients do, they don’t necessarily trust physicians or think highly of them. Additionally, Trombetta noted the incidence of violence against healthcare professionals is high enough that there is a specific term describing it, “Yi Nao,” which translates to healthcare disturbance (see bit.ly/2FPubCN and nyti.ms/2NRhGj3).

The causes for this violence have been reported to be poor investment in the health system and in training and paying doctors. Those can lead to medical errors, corruption, and poor communication between HCPs and patients. Other factors include negative media reports, poor public understanding of medicine, unrealistic patient expectations about treatments, and the high out-of-pocket healthcare expenses for families.

It is this lack of patient understanding around medicine and innovative treatments that concerns Yan. “I see the next 10 years as a gold rush in China in regard to innovative medicine,” he says. “But I also see that people don’t understand how long it takes to develop a drug, and how much the costs can be, even for biosimilars. Where will the funding come from? Do I think about that a lot.”

The promise
IP issues in China are of dwindling concern, again addressed by more robust legal practices. As these videos from our senior editor attending the JPM Healthcare Conference in January show (bit.ly/2WuE42s), most executives are not alarmed over IP anymore. It’s not an overnight phenomenon that innovation, regulatory, IP, and funding rules changed in China, and many initiatives have been ongoing and are now gaining speed from these new market forces.

One trend not going away is less tangible, but clearly a force. As Yan observes, “There are many people like me, who left the country to study abroad to learn and work for 10 or 20 years and they come back to China with the skills, knowledge, and the entrepreneurial spirit.” That is the promise for the future of pharma in China.
Mixed Outlook for Sector
Momentum, uncertainty shape economic picture

By Michelle Maskaly

Tempered optimism.

That’s how experts describe the outlook for China’s life sciences economy despite seeing a slowdown in other industries across the country.

In fact, investment activity in China’s life sciences set new records across the board in 2018.

“The outlook for China biotech is very positive at this point. All areas are up significantly from 30% to 50%,” says Greg B. Scott, founder and chairman of ChinaBio Group. “There was over $44 billion raised in venture capital (VC) last year and over $17 billion invested in life science.”

During a presentation at the China Showcase at the J.P. Morgan Healthcare Conference last month, Scott dubbed the current climate the “golden era of healthcare in China.” According to numbers provided by the group, from 2017 to 2018, VC investment in the Chinese life sciences rose 36%, M&As spiked 53%, IPOs 41%, and partnering 65%.

Scott said the predominant factors driving these investment numbers included robust government support; significant VC and private equity funding; sweeping regulatory changes; strong talent base, and a major shift in socioeconomic trends.

“Overall, the China economy is strong compared to almost any other major economy,” Scott told Pharm Exec. “Double-digit growth [is expected] next year in biotech and medical devices, and the VC climate is also strong.”

Not everyone agrees that the record-setting growth in China’s life sciences is going to continue at the same pace. “We have not slowed down as a firm, but the industry has become more cautious,” contends Jonathan Wang, senior managing director at OrbiMed, a private equity and VC firm. “Numbers are still very promising the last 18 months or so, but China is facing major challenges—many things are happening at the same time and those can cause uncertainty. Don’t be fooled by the great numbers you have seen over the last 18 months. There are major uncertainties. But, in the longer run, it’s very optimistic.”

One of those uncertainties is the valuation of new biopharma companies. “The last few years, China life sciences has been in a valuation bubble,” says Victor E. Tong Jr., a partner at Decheng Capital, an investment firm that provides capital and strategic support to early-stage biotechs. “We are going to see valuations trickle down and become normal this year.”

Tong, whose company has offices in Shanghai and Silicon Valley, says another factor poised to impact the life sciences in China is the fact “large pharma didn’t do as many deals last year.” While some consider this a negative, Tong believes it could actually be advantageous for the industry. “They have some capital and if you combine that with valuations coming down, you will see more M&As this year,” he says.

No longer emerging
If it seems like China has catapulted into the pharma and biotech spotlight, it is because it has. Despite large pharma companies having a presence in the country going back years, the industry wasn’t taken very seriously, many believe. Riddled with regulatory issues and IP concerns, China has long been referred to as an emerging global pharma market. According to experts, however, it’s no longer emerging—it’s here.

In addition to the host of factors cited by ChinaBio, one major driver many are attributing this surge to is talent. Talent is an increasingly important ingredient in the biopharma ecosystem in the US, and it’s not any different in China. More and more science, data, and business professionals who have ties to China but either grew up in the US, were recruited by US companies, or decided to continue their education in America, are being courted by Chinese organizations pursuing operations in China.

“China’s time has come,” Christian Hogg, executive director and CEO of Chi-Med, a biotech, told Pharm Exec during a meeting at the JPM conference. “Patients are benefiting greatly, but investors and companies involved are going to have to be really clever in how they execute their business models. But the area has great potential.”

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CFIUS Reform’s Impact on Biopharma

What the new rules mean for Chinese-related investments and acquisitions in the US

By Peter Young

One of the prominent topics in the last few years has been the rise of the Chinese biopharma industry. One aspect of that rise has been the investments and acquisitions made in the US by Chinese biopharma companies and investors. That activity has been heavily impacted by the recent changes in the rules and laws affecting the activities and scope of the Committee on Foreign Investment in the United States (CFIS), particularly with regard to the criteria for acquisitions and investments in US organizations that are in “sensitive” sectors.

CFIUS was created in 1988 by the Exon-Florio Amendment to the Defense Production Act of 1950. CFIUS’s authorizing statute was amended by the Foreign Investment and National Security Act of 2007 (FINSA). This statutory framework authorizes the president of the US (through CFIUS) to review “any merger, acquisition, or takeover ... by or with any foreign person which could result in foreign control of any person engaged in interstate commerce in the United States.” CFIUS, therefore, has been in existence for decades and was originally established to review foreign investments and acquisitions of entities that related to national security. The definition of national security had some nuances, but CFIUS did not typically target biotechnology. In addition, the regulations focused primarily on control acquisitions of companies, not minority shareholdings.

Although the new rules supposedly cover any foreign company or investor, it is clear that the concerns of the US government are focused on Chinese, Russian, and related countries.

The recent changes are perceived to have been prompted by the very aggressive investment and acquisition activities of the Chinese in the last couple of years and the designation of a number of industries by the Chinese government as industries that they planned to achieve leadership positions by 2025. This policy was widely known as “Made in China 2025.” Interestingly, biotechnology was one of the industries specifically on the list of industries in “Made in China 2025.”

What has actually changed with the new rules? There are several changes, but the rules now allow the US government to block acquisitions of minority investments, not just control stakes. In addition, they have expanded the definition of foreign interest to include not only the location and nature of the general partners or investing entity, but also may include who the limited partners are. So, for example, if a Chinese company or venture firm makes an investment in a US biotech that would result in a 10% ownership stake on a pro forma basis, that could be a prohibited investment. In addition, if a US venture firm has a Chinese limited partner who has invested in the US venture firm (or any foreign limited partner), the US venture company could potentially be treated as if they were a foreign investor.

The regulations require a filing with regard to an investment or acquisition in “critical technologies,” otherwise it is voluntary. However, the government has the right to investigate the investment or acquisition even if the party does not file. In addition, there is no defined deadline for when a ruling is owed by the government. In the end, if there is a CFIUS ruling against the transaction, the transaction can be disallowed and a penalty up to the value of the investment or acquisition can be imposed.

The filing itself, which carries a filing fee cost, is not a major obstacle. There is an onerous scenario, however, where the US government may not rule in any reasonable timeframe and the transaction can be disallowed after a long period of time has passed.

The new rules have resulted in a major cooling of investments in and acquisitions of US biotech/biopharma companies by Chinese entities and some non-Chinese foreign entities. The perceived risks are too high for both the company selling or seeking equity funds and for the Chinese entity.

How, then, have the Chinese biopharma companies and Chinese-related private equity and venture firms adjusted? In most cases, they have focused their energies elsewhere, including by investing more in China and other countries. In addition, they have placed a heavy emphasis on in-licensing of products and drug candidates from the US biopharma companies.
Opening the Golden Door

The talent and tenacity of immigrants can help drive the life sciences industry into the future, if we have the will and the wisdom to encourage it. The child of the woman who cleans your office every night might just discover the drug that saves your life in 30 years.

It’s our responsibility as an industry to improve the quality of care for patients around the world at the fastest possible rate, day after day and year after year. That is how pharma companies earn the right to continue to exist and thrive. If we are to achieve that task, we must not limit ourselves to only being advocates for our patients or our regulatory or R&D prowess, or even ourselves. Patient advocacy will always and should always come first. But we must also be advocates for the people who will help us achieve that task tomorrow, and next year, and in five years, and in 30 years.

Those people might be nearby, or they might be thousands of miles away, in an obscure village in a developing country. They might be well-educated and motivated and aiming for a work visa to the US, or they might be struggling to escape the worst kind of poverty and despair. Or they might not even have been born yet. But wherever they are, it’s past time for us as an industry to speak out loud for those people, those immigrants who—combined with the powerful engine of American innovation and ingenuity—will drive us to a healthier future if we let them. Not because it may be the right thing to do, but because it’s the smart thing to do. Sometimes right and smart, as it happens, may just be the same.
WE LIKE TO SEE YOU EXCITED ABOUT PURSUING YOUR DREAMS

That is why, for almost 90 years, we have been providing the therapies you need: cutting edge treatments for disabling conditions and rare diseases, as well as treatments for everyday illnesses. On all 5 continents around the world, we want to encourage you to live life fully.

TO LIVE... AND TO DREAM.
With Spain now squarely on the road to economic recovery following the ravages of the global financial crisis, multinational pharmaceutical companies are seeing the country as a top-tier investment destination once more thanks to a much-improved market access scenario, high quality, but affordable manufacturing capabilities and an enviable clinical research base. Gone are many of the forced price reductions and ejections from the reimbursement list that coincided with the implementation of successive austerity programs. Instead Spain today stands proud as the tenth largest pharma market in the world with a valuation of some EUR 26.15 billion (USD 29.55 billion) in 2017 according to BMI.

“Overall the Spanish life sciences sector has exhibited great resilience having initially endured quite a hammering: for the past three years, the overall value of pharmaceutical sales in the hospital segment expanded at a rate of 3.3 percent while retail sales increased 2.2 percent... I genuinely cannot think of any other European market that has enjoyed an analogous growth trajectory,” confides Humberto Arnés, the director general of Farmaindustria, Spain’s leading pharmaceutical industry association.

Timmo Andersen, senior vice president and head of Europe, Canada and Australia at Boehringer Ingelheim very much concurs. “Spain is a great country to be operating in at this moment. Growth in the local pharmaceuticals market is outpacing much of the rest of the national economy at around three to four percent and moreover this is happening on a consistent basis,” he enthuses.

A visible improvement to the market access context has naturally been a decisive factor in this turnaround in investor confidence. “In addition to market growth, two other important indicators reflect positive change: product availability and the timeframe taken for a product approved by the EMA to reach the Spanish market. We had dramatically dropped behind for both indicators during the crisis, but are thankfully now back in line with markets such as Italy, France and Germany,” explains Arnés.
Many country managers of originator drug MNCs now perceive the Spanish life sciences space to be competitive again within its region. “I actually would go as far as to say that Spain has attained a satisfactory level of market access: comparing the percentage of drugs approved by the Ministry of Health and the time frame it takes to gain full market access for innovative medicines, we can now conclude that Spain sits amongst the more efficient European markets,” affirms Ángel Fernández, president and managing director of MSD Spain and Portugal.

The strong performance that many affiliates are registering is also serving to pep up investor sentiment. “Expectations for the local market are riding high. A few years ago, our affiliate actually won an award internally for being the most dynamic market within Allergan’s entire international division and we have been registering double-digit growth every year, which is rather unprecedented and simply not normal for a settled, Western European market,” radiates Allergan’s director general for Iberia, Fernando Álvarez.

Little wonder, then, that more and more multinational pharma firms are contemplating presence on the Spanish market as a necessary and logical step in their European internationalization strategies. “Practically any drug maker worth its salt that is looking to build a strong reputation in Europe must position themselves in the EU-5, and that includes being in Spain,” argues Sergio Serra Ripol, managing director of Tillotts’ local affiliate. “The fundamentals of this market are pretty compelling: a positive economic swing, rising GDP, sectoral growth, an increasing envelope of life science investments backed by large volume of KOLs and medical professionals that are world-renowned within their therapeutic area, and to cap it all off, a universal healthcare system that is one of the best in the world in some aspects!”

Indeed, examples abound of relative newcomers to Europe making it a priority to establish on-the-ground footprints in Spain. “Purely from the market size perspective, Spain constitutes a very mature and strategically significant market where practically all the major firms are present. It therefore follows suit that the two affiliates that our Group maintains to date on the continent should be located in Spain and France,” reveals Juan Luis Fernández Balaguer, general manager of Laboratorios Combix, subsidiary of Zydus Group.

Participants in the Spanish market certainly tend to paint a picture of a jurisdiction that is broadly welcoming towards innovative medicine and ready to cater for ambitious product launch tempos. “I think that Spain has become very professional in rewarding novel innovation. From a regulatory adjudication standpoint, we detect a real shift towards conducting technical assessments, rather than merely comparing new treatments to what already exists within the marketplace. Innovation is really being evaluated on an individual basis, which is excellent news for genuine innovators just so long as...”

**SPEEDY PRODUCT-launches**

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**TOP 20 PHARMA COMPANIES IN SPAIN (TOTAL MARKET)**

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<th>Source: IQVIA</th>
<th>% Market Share</th>
<th>% PPG Previous Year</th>
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<td><strong>1.</strong> GLAXOSMITHKLINE</td>
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<td><strong>2.</strong> CIFRA</td>
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<td><strong>3.</strong> SANOFI-AVENTIS</td>
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<td><strong>12.</strong> JANSSEN CILAG</td>
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<td><strong>19.</strong> ASTELLAS PHARMA</td>
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<td><strong>20.</strong> KERN PHARMA</td>
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<td><strong>TOTAL OTHERS (2335)</strong></td>
<td>55.2%</td>
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MAT 04/2018 (last 12 months): April 2018 - May 2017
% PPG: Growth over the same period of the previous year
% Market Share € PVP: percentage of market share based on sales euros public price
they can adequately demonstrate added value,” posits Shionogi’s Ramón Villamarín Valdenebro.

Allergan’s Fernando Álvarez wholeheartedly agrees, pointing to highly innovative “needle movers” (i.e. game changing products) that his company has managed to successfully introduce to the local market including Ozurdex®, which offers a novel solution to combat retina swelling caused by conditions such as diabetic macular edema, and CoolSculpting®, a groundbreaking cryolipolysis-based technique for reducing stubborn fat without surgical intervention. Being able to achieve this likewise contingent upon proof of value delivery. “In the Spanish market, products must be more sophisticated and encompass a larger spread of requirements, not only the needs of the doctors, but equally of the system as a whole and patients. Efficiency must work alongside results, not
just one or the other. That’s why we are so attentive to compiling evidence such as pharmaco-economic reports that indicate economic impact, as well as the optimization of care processes,” he reveals.

“We’ve witnessed somewhat of a paradigm shift in terms of the process for evaluating the benefits of new therapies,” confirms Baltasar Lobato, partner for the health & life sciences advisory practice of EY. “Traditionally the main customers for pharmaceutical companies were doctors and the emphasis was on comparative medicinal value and clinical performance. Nowadays, as the healthcare provider looks more and more towards sustainability, they are tilting towards the best treatment in terms of overall end outcomes and cost and therefore companies must negotiate directly with payers. As a consequence, the traditional network of large sales teams is giving way to smaller market access teams including pharmaco-economists talking specifically to government officials.”

Certainly, the rewards for companies that go about it in the right way can be considerable. Many of the MNCs are boasting remarkably good product launch rhythms in Spain. Pfizer has introduced five new innovations to market in 2018 alone, while French mid-cap, Ipsen, has impressed in the efficient manner in which it successfully launched its revolutionary oncological product for renal cancer, Cabometyx, in under a year. “Bringing a sophisticated product like Cabometyx to market in a mere nine months is testament to our rapid reaction speeds, agile biotech-style mindset and an accommodating contextual environment…Drug developers often bemoan the complexities of bringing portfolios to stagnating European markets, but we have managed to buck this trend by proving that it is possible to speedily and efficiently execute product launches. I personally believe that the secret is properly understanding the operational landscape and the needs of the target health system,” recounts Guillermo Castillo, managing director of Ipsen Iberia.

“We very much hope that our experience in launching Cabometyx can serve as a showcase example of the possibilities within Europe to introduce innovation despite the severe financial constraints on health systems. Being very transparent and upfront in terms of pharmaco-economics, we commenced negotiations submitting the dossier in December and received approval from the Spanish authorities in March. It was the first time in my entire professional career that I had a process surpass the infrastructure required to actually roll out the project!” he remembers.

FRAGMENTATION AND DEVOLUTION OF DECISION-MAKING

That’s not to suggest, however, that Spanish market access is all sweetness and light. One complicating quirk of the Spanish system is the seemingly inordinate powers vested in regional authorities. “Spain is one of the most decentralized countries in the EU and consequently one of the unique features of the market is the fragmentation linked to the country’s 17 autonomous regions; each of which leverages its own jurisdiction over the organization and delivery of health services within the territory,” observes Tilloots’ Sergio Serra Ripol. “This might well bring some advantages, as it allows the health system to stand closer to the end user and deliver tailored solutions, but it definitively poses a market access challenge for the industry and even more so for smaller specialty outfits like ours,” he laments.

“Although the national approval time is relatively quick, practical access can be impeded by this territorial fragmentation,” concedes MSD’s Ángel Fernández. “In my opinion, there are simply too many bodies – too many moving parts – that are making individual analyses.”

Indeed, “there is ample evidence to suggest that excessive dilution of decision-making powers is breeding inequality and distorting the balanced incorporation of science and innovation,” notes Bayer’s CEO, Bernardo Kanahuati. Certainly, wild disparities between healthcare expenditure and provision can be witnessed across the different geographical zones. For instance, the
Against an alluring backdrop, big name pharma brands are now starting to spend heavily on in-country manufacturing, development and shared service facilities. Boehringer Ingelheim, for its part, has chosen to situate key global functionalities in Spain, including an IT support center as well as three regulatory affairs centers. Furthermore, in June 2017, the company announced a EUR 130 million (USD 150 million) investment in its Sant Cugat del Vallès manufacturing facility in Catalonia.

Noting the rationale behind these big-ticket Spanish investments, BI’s Timmo Andersen points out that, “Spain has exceedingly high youth unemployment. However, the country simultaneously possesses some of the best business universities, technical schools and hospitals. This means that it is very easy to source affordable, but high-quality talent.” He continues, “manufacturing in Spain is significantly cheaper than it would be in Switzerland or our home country of Germany, and yet we can still produce top notch, reliable products suitable for export all around the globe.”

Another German pharma heavyweight, Bayer, has been following suit pursuing heavy capital injections into upgrading its hardware and rendering Spain a keystone of its global supply chain infrastructure. “If we take a look at the numbers for 2017, for example, overall, we invested EUR 33 million (USD 38 million), EUR 13 million (USD 15 million) of which we invested in infrastructure, among other projects, improving plant quality and updating office spaces. The remaining EUR 20 million (USD 23 million) was invested in R&D,” recounts CEO, Bernardo Kanahuati. Its API plant in La Felguera in Asturias produces the entire group’s acetylsalicylic acid, the active component of Aspirin. The company’s production plant in Alcalá de Henares, Madrid, meanwhile, constitutes the sole Bayer plant to produce soft gelatin capsules and doubles up as an important site for innovating new encapsulation technologies.

In a similar vein, Pfizer’s production plant in San Sebastián de los Reyes, Madrid, is notable for being the only Pfizer plant in the world that manufactures, packages and distributes recombinant products for the treatment of hemophilia A and B. “This is a critical facility because we distribute products manufactured in this plant to 15,000 patients spread 75 different countries,” explains CEO, Sergio Rodríguez.

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Innovation and Commitment
Cardiva is one of the leading distribution companies of products for the healthcare sector which works to improve patient quality of life.
Basque Country, Principality of Asturias and Community of Navarre spend over 30 percent more on health per capita than the region of Andalusia. Meanwhile, according to the European Observatory on Health Systems and Policies, the proportion of patients on waiting lists is up to five times greater in some regions than in others. Patients in regions like Catalonia and Castilla-La Mancha wait on average more than 160 days for surgery, compared to less than 50 days in other autonomous regions.

Dr Josep Tabernero director of the Vall d’Hebron Institute of Oncology and head of the Medical Oncology Department at Vall d’Hebron University Hospital, adds that the continuum of care is stronger in the larger regions. He notes that “Smaller regions often need help with patients in terms of special diagnostics, whereas larger communities often have better facilities to offer optimal treatments. In the larger regions, the continuum of care is good because primary care is good, and there is good interaction between the primary care and the hospitals.”

These differences also play themselves out when it comes to the therapies on offer, especially ones with a limited patient group. “The European Commission has approved some 53 orphan drugs, but only 18 are securely reimbursed here in Spain across all the regions. Moreover, even if the regions approve the drug and agree on the reimbursement, then the individual hospitals may still think differently,” regrets José Manuel Rigueiro, former general manager of Actelion. “This is why Spain is essentially an ‘access’ market, meaning that companies typically devote more resources to market access than in other countries, even with a similar size,” he adds.

So, what practical strategies can companies deploy to navigate this anomaly? “It all starts with mapping out and establishing a standard profile for each region... Regions display massive discrepancies and a local solution is needed to solve a local problem: some are tremendously advanced in what they are doing and others are laggards. Therefore, we have to be flexible enough to adjust to their capabilities and the underlying infrastructure on the ground. One local fix that Ipsen has come up with – and many companies of our size are doing the same – is to combine the positions of the access and key account manager into a single job under which the holder is accountable for everything that is happening in these areas of responsibility,” discloses Guillermo Castillo.

“It all starts with gaining the situational intelligence. To operate your business effectively under these circumstances, it is critically important to understand each of the local markets, while gradually building the relationships with key opinion leaders. Once you have amassed this know-how there are still human, logistical and technical difficulties to surmount if you are a small or mid-size firm. I remember a delay of around six months in the effective commercialization of one of our products in one specific small region, due to a mere technical particularity in their IT prescription system, which we should have probably identified earlier,” admits Tillots' Sergio Serra Ripol.

Allergan, meanwhile, has come up with its own formula to surmount the onerous resource requirements to deal with this level of complexity. “We have been reorganizing and transforming our market access capabilities with a focus on the major needs of key stakeholders in the system. Essentially, we are assigning our market access personnel to clusters of regional markets that exhibit similar characteristics, so they can work in more than one state, rather our having to maintain 17 separate teams for each of Spain’s autonomous communities,” says Fernando Álvarez.

Others, however, believe that the impact of the regional dimension can be overstated. Paolo Cionini, vice president for Europe South and country manager for Spain and Portugal at LEO Pharma, notices parallels with the devolved authorities in Italy. “It may look quite daunting to begin with, but Spain is actually a little less complicated because there is more fluidity. At all administrative levels, it is easy in practice to engage in dialogue with the authorities in Spain which in turn makes it comparatively simple to identify common solutions and conclude deals.”
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Javier Alvarado, general manager, Mundipharma

This relationship building approach has been key for Mundipharma, headed by general Manager, Javier Alvarado. He acknowledges that the “Spanish pharmaceutical market has managed to maintain a favorable level of access to innovative medicines by maintaining control of pharmaceutical expenditure that guarantees the sustainability of the system”. Therefore, his strategy is based “on dialogue and collaboration with national and regional administrations which are responsible for health competencies. We have a very clear direction to focus on innovation and commercial excellence through building partnerships. We consider it essential to facilitate patients’ access to innovative drugs, ensuring the sustainability and equity of the system.” This has allowed the company to “recently launch Flutiform K-haler®, a new drug for the treatment of asthma. In the area of analgesia, we are aiming to obtain reimbursement of an inhaled analgesic for the relief of acute pain in the field of medical emergency”. Furthermore, one of the affiliates key objectives in 2019 is to facilitate “access to new medicines and aligned with this priority we hope to launch two new innovative drugs in the first quarter of 2019”.

People and ideas for innovation in healthcare

Chiesi

People and ideas for innovation in healthcare

STAGNATION IN THE GENERICS SEGMENT

Another peculiarity is Spain’s sluggish generics market. “The generics market is growing at 4.5 percent but still, the penetration for the sector is relatively low at approximately 42 percent of units sold and 24 percent of total sales revenue. In a healthy market, the penetration in value should be around 40 percent,” attests Combix’s Juan Luis Fernández Balaguer.

“To be honest, we are slightly worried about the current situation, because the Spanish generics market has stagnated and not grown at a decent rate for quite some time now. The primary cause of this lack of penetration is the absence of a clear price differential between the reference medicine and the generic product, which is mandated by legislation. According to Spanish law, once a drug comes off patent, the originator and generic are priced equally, which thoroughly distorts the market dynamics. In fact, if you rewind a decade to prior to the implementation of such rules, we were instantly achieving around 70 percent generics penetration when a drug came off patent. Now we are lucky if we reach 10 to 15 percent!” argues Enrique Ordieres, president of CINFA.

For this reason, the Trade Association of Generic Producers (AESEG) has been vigorously lobbying for the abolition of this stipulation. “We consider the regulatory framework in force to greatly disadvantage our members and create artificial imperfections within the marketplace. Even many originator drug developers could be interested in reversing these decisions because not all are happy to have to lower the price from the first day of the patent expiration and go to the private market with a low price,” reasons Ángel Luis Rodríguez de la Cuerda, AESEG’s secretary general.

Additional hurdles are also apparent. “While it is mandatory by law for doctors to prescribe treatments by Non-proprietary Name, not all the 17 regions implement it in an orthodox manner, leading to a situation whereby in some autonomous communities, penetration is very high, and in others it is very low,” reflects Carlos Teixeira, CEO of TEVA in Spain and Portugal.

Not only is a stalled generics market bad news for the national health system in terms of squandered cost savings that could otherwise have been reinvested into financing innovative medicine, but also it is unfair for the generics players who contribute so much to the national economy. “Let’s not forget that of every ten generics consumed locally, seven are produced in Spain and this something that brings a lot in terms of GDP growth,” reminds Teixeira.

“The Spanish generics industry, despite its difficulties, has saved Spain EUR 20 billion (USD 23 billion) over the past two decades and the government needs to realize that the opportunity for us to save them even more exists,” reinforces Enrique Ordieres.

All of this also colors the composition and make-up of the local generics landscape. “Our main competition in Spain is not only coming from international companies, but also from national generics companies. Out of the five most important generics players in Spain, three of them are national companies. This is a unique market in Europe. To differentiate ourselves against
these local competitors we are compelled to maintain a strong patient focus,” muses Joaquín Rodrigo, general director Iberia of Sandoz.

The homegrown Spanish players are equally forced to tweak their business models. “Our generic products are the same as our competition and are offered at the same price. Therefore, we must in some way differentiate ourselves in our interactions with the health community and be smarter and more agile; a challenging task in a saturated generic ecosystem,” elucidates Joachim Teubner, general manager of Aristo Pharma.

“I believe that the significant pricing pressures being applied will necessitate a lot of consolidation in the generics field and companies that are not back integrated with self-manufacturing, will not survive. Already we see the market beginning to shrink and numerous M&As,” he notes, while pointing out that the fact Aristo manufactures its own products in Spain, via its production arm, Medinsa, means the company “can offer attractive prices in an agile manner, which is well aligned with the competitive and low-margin nature of the Spanish generics business.”

Meanwhile other players, like Kern Pharma, have been resorting to diversifications as a way to spread risk and mitigate exposure. “Even though we are mainly a generics company, we consider it prudent to hedge risk and cover other growth possibilities in the market. We envisage challenges in the future, so we knew we had to be prepared, especially for establishing an OTC base and have even managed to launch a sports supplement line,” candidly details managing director, Raúl Díaz-Varela.

BETTING BIG ON BIOSIMILARS

Some of the more sophisticated generics companies are thus already beginning to look beyond the prevailing local market woes and start vesting their hopes in the embryonic biosimilars segment. “It is clear that the generics market has matured and lost some impetus, so the growth momentum lies more with biosimilars. With patents beginning to expire on wide range of biologic therapies we are detecting a palpable increase in interest in biosimilars,” acknowledges Joaquin Rodrigo of Sandoz.

Sandoz, in fact, enjoys the distinction of being the first company to commercialize a biosimilar in Europe including Spain, namely the growth hormone Omnitrope and is intent on maintaining its first mover advantage in this field so has been playing a lead role in preparing the groundwork locally. “It is vital that we avoid the mistakes Spain made when generics were first introduced to the market, such as misconceptions and false perceptions of products. The idea is to involve the whole value chain right from the beginning and to shape the biosimilars ecosystem hence our contribution to the establishment of a dedicated Spanish biosimilars association (BioSim),” adds Rodrigo.

“At the moment, we have 39 approved biosimilars in the EU belonging to 15 molecules, while in Spain we have 26, which is mainly due to the time lapse between the EU authorization and the confirmation of the Spanish Agency approval, patent expiry dates or the particular interests of each marketing authorization holder,” remarks Regina Múzquiz, director general of BioSim.
Quite a few big name local entities are now belatedly getting on the bandwagon. Kern Pharma, for example, has signed an eye-catching partnership with Celltrion to bring such molecules to market. Meanwhile Reig Jofre has joined forces with the biotech, LeanBio, to set up a new entity called Syna Therapeutics. “This project is international so we would sell wherever we detect demand, whether in Spain or indeed the rest of Europe. We need to fine-tune the model but the industry will undoubtedly grow. It is a model that cannot be avoided. For the rest of the world, it makes sense from a pure access perspective. Many countries have not had access to certain biologics because they were too expensive. Biosimilars are the answer to that,” confidently declares Reig Jofre CEO Ignasi Biosca.

Others, however, have noticed the relatively low local penetration rates in the areas in which biosimilars are currently present in Spain, such as oncology, where they register around a mere five to eight percent, far below their potential.

Despite the biosimilar market needing a clearer direction, the country has witnessed its own innovation in the area. Cinfa recently developed and achieved EMA approval for a biosimilar therapy, Pelmeg® before selling the business arm, Cinfa Biotech, to Mundipharma. This, for Mundipharma’s Javier Alvarado, is “strategically very important for us. This expands our biosimilar platform beyond commercial excellence to development. Furthermore, for Alvarado, it allows the company to play an important role in creating accessibility for innovative therapies; “an essential factor in guaranteeing the sustainability of the healthcare system.”

A PREMIER CLINICAL TRIALS DESTINATION

Innovative drug developers have few such concerns. On the contrary, they have become increasingly enthused by Spain’s prowess as a clinical trials venue and R&D hub. “Spain seems to be going through a golden age for clinical research: right now the country is participating in more than 20 percent of the almost 4,000 clinical studies carried out each year in Europe and is vying with the UK to become the preferred second choice destination within the EU27 after Germany,” attests Ion Arocena, CEO of the Spanish Biotech Association (ASEBIO).

Homeopathic Medicines: Changing the Narrative

In late 2018, new minister of health, Maria Luisa Carcedo, made the move to blacklist thousands of alternative medicines in a bid to crackdown on products considered to have “no scientific basis.” With this list came heavier scrutiny towards a group of treatments that have been utilized for decades: homeopathic medicines. As a result, the homeopathic producers of any products on a list of 2008 medicines, have until April 2019 to prove that their remedies clinically work.

Leading the fight against the new wave of criticism is global homeopathic leader, Boiron, headed in Spain by general manager, Eduardo Barriga. The French-based company works heavily in generating clinical data to back up their claims, though Barriga feels, “there is heavy criticism [of homeopathic medicine] in Spain which is undeserved. Spain is a market where the homeopathic regulations were previously not aligned with that of the EU, but they are heading in the direction of being regulated in the same way. As the market leader, we want to be regulated in the spirit of the European laws.”

For Barriga, “it is imperative that stakeholders have an open mind to homeopathy and “for those who have yet to consider the added value of homeopathy in their medical offerings; open your mind, your patients are looking for these new health solutions.” To catalyze this process, Boiron is working to educate Spanish pharmacies and doctors, with Barriga believing that “if we can apply what has been done successfully in markets where homeopathy is valued, like France, the dynamics here can reach the same level within the next five years.”
Many multinationals have been unequivocal about ramping up their in-country R&D presence. “Within the last two years, we have signed agreements with two leading research institutes and two leading universities. We are conducting some 55 clinical studies and are working hard to convince HQ to invest even more into Spain’s clinical operations, specifically phase I and phase II studies,” declares Marieta Jiménez, president and general manager of Merck.

MSD’s Ángel Fernández adds that “we consider Spain to be a top worldwide clinical research platform and some 80 percent of MSD trials are executed in some shape or form here.”

Some globally renowned, star products have also been conceived in Spain. “One of Ipsen’s Spanish affiliate’s main claims to fame has actually been its part in the creation of champion product, Somatuline, used for the treatment of neuroendocrine (NET) tumors and the hormonal disorder Acromegaly. Somatuline, which was launched in the US three years ago and continues to undergo sequential innovation, was originally developed here at the local site,” laughs Guillermo Castillo.

What though, makes Spain such an appealing proposition for this type of activity relative to its peers? “The country’s many excellent researchers, practitioners, clinicians and the presence of large health infrastructures, give it an edge as well as the deep talent pools of expertise in therapeutic areas like cardiology and oncology,” claims Bayer’s Bernardo Kanahuati.

Pfizer’s Sergio Rodríguez adds that “Spain is also comparatively fast in approving the different stages of clinical trials while the size of the market means you can generally access the patient groups you require.”

The affordability differential also counts of course. “The trade off between efficiency, cost and reliability works out: we can depend upon and place our trust in Spanish researchers and the cost comes in substantially cheaper than other sophisticated markets such as France and Germany,” shrewdly calculates TEVA’s Carlos Teixeira. “A full preclinical to post clinical program can be carried out in Catalonia for half the cost or less than in other key regions in Europe, the UK, or the US,” agrees Jordi Naval, CEO of the Catalan Bio-Region (Biocat).
Simultaneously the existence of a fully-fledged biotech hub situated in Catalonia has helped to keep the quality of clinical research high. “Today, more than 60 percent of all the healthcare and biotech innovation of Spain is happening in and around Barcelona and there is a comprehensive professional ecosystem in place to support life sciences activities right along the value chain encompassing R&D, training, regulatory, CMO, licensing, IP and much more besides,” points out Naval. Even the funding landscape is much more evolved than hitherto. “Between 2015 and 2017, Catalan start-ups in the healthcare sector attracted EUR 340 million (USD 392 million) in investment, three times more than in the 2013-2015 period. The capital raised through rounds of investment with international participants has also doubled in recent years, from EUR 85 million (USD 98 million) in 2013 to EUR 211 million (USD 243 million) in 2016 to 2018,” he discloses.

“Historically, venture capital (VC) investment in Spain was drip fed to life science pioneers, though but we have been noticing a decisive shift towards larger funding rounds reaching tens of millions for early-stage companies and sometimes even from scratch. Furthermore the ‘build-to-buy strategy,’ when investors invest in off-balance R&D for a company, with the option of acquiring the company later on is becoming much more common and

Procare Health: Bringing Clinical Data to Natural Medicines

Yann Gaslain, CEO, Procare Health

Clinical evidence is a hallmark of the classic pharmaceutical model. Yann Gaslain, CEO of Procare Health, a Catalonia-based company focused on women’s health, is bringing this clinical concept to natural products that have never been tested in this way. The problem for Gaslain is that many key opinion leaders still see the idea of natural products being clinically proven to be a foreign concept. To counter this we must work with them to open their minds. We are open to discussing this information in a constructive manner.”

This strong R&D focus has led to strong results since the company was founded in 2012, backed by the star product Papilocare “the only product that helps women manage the HPV virus, the leading cause of cervical cancer in woman”.

Furthermore, the company is working with the “California Nanosystem Institute of the University of UCLA for the development of an innovative Cervix on a chip, a technology they have developed for other organs. We will then be able to conduct experiments on real tissue, rather than the traditional model via animals or plates. In turn, results will be more accurate and allow us to measure the side effects in real time, as a preliminary step to expensive but necessary clinical programs.”

This innovation has allowed the company to establish an exciting international footprint in a short period of time. Gaslain notes that Procare already has partnerships with “Shionogi in Italy for Papilocare and Libicare, Gedeon Richter in Eastern Europe and Besins Healthcare for Latin America.”

The next step is to enter the US market, though this still requires talks with the FDA. If positive the company “will set up a legal US entity and look to possibly partner with a local distributor,” explains Gaslain.
is testament to the maturing of the ecosystem,” believes Joël Jean-Mairet, general partner at Ysios Capital.

Moreover these successes have all emerged despite the virtual absence of public funding for R&D. “The overall public spending on R&D is only 1.2 percent of GDP compared to the average 2.3 percent throughout Europe or countries like Germany and the UK which are well over 3 percent. Part of the challenge with funding comes from the issue that one-third of the GDP expenditure for R&D is in the form of low-interest loans. It is impossible for a researcher to pay back the loan when he does not have a model of revenue; basic research only works with direct investment,” argues Gijs Jochems, general manager of Promega, a company specializing in molecular biology, protein analysis and expression, which itself had to reconfigure its business model in the wake of a sharp decline in public financing for R&D.

**MAGNIFICENT MID-CAPS**

Spain’s high-performance midcaps have hit upon a variety of strategies whereby they target niches that Big Pharma has not covered and play to their strengths. As Oriol Segarra of Uriach notes, “filling a glass with big stones will create holes for small pebbles to fit in. Big Pharma companies may have areas that fall under the radar which can be taken advantage of by smaller outfits.”

For family-owned Laboratorios Rubió, their strategy revolves around close interaction with healthcare practitioners and shrewd acquisitions of products at different stages of their life cycle. Executive President Carlos Rubió explains that, “We are always looking for the next move. For example, we licensed a product that was previously been licensed to Bayer, and within two years had doubled the sales. This is all based around a close-knit interaction with doctors, and this is a strategy we look for with our international partners abroad. Furthermore, we see growth by acquiring or licensing products at the end of their life cycle. This means they do not require an abundance of marketing as they are already well
Private Healthcare: Open for Negotiations

The Spanish healthcare system is universal. “In principle, this universality would eliminate the need for a private health system,” explains Carlos Rus Palacios, general secretary of ASPE, the private hospital and private healthcare association. “However,” continues Rus Palacios, “private healthcare exists, serving more than 12 million people and represents more than 30 percent of healthcare activity in Spain.”

In terms of innovation, “over the last 12 years, most technological innovation has been coming from the private sector,” points out Dr Juan Abarca Cidón, president of HM Hospitales, a leading local private healthcare provider. “During the crisis years, the public sector was severely impacted, and investments in this area have suffered. I believe that there needs to be an agreement between the government and private sector to better facilitate innovation collaboration in order to allow more patients access to the latest technologies which can only be found in private health centers.”

“In many health systems, citizens with higher financial status enroll in private insurance schemes in order to reach access to what is not offered by the public system. Contrarily, in Spain, we have a public excellent healthcare system, which completely covers all beneficiaries. The private system is not a fragmentation of healthcare in Spain; there continues to be a link between the two sides,” underlines Fernando Prados Roa, deputy minister of health at SERMAS, the Madrid system of healthcare centres. “Around 20 to 25 percent of our activity is done with our supervision but performed by private management. This allows for homogenization since our indexes are similar, patient satisfaction is high, but also allows for transparency,” elaborates Enrique Ruiz Escudero, minister of health for the community of Madrid.

Several companies are using the private sector’s openness to innovation to their advantage. Chiesi recently struck an agreement with HM Hospitales for the provision of Holoclar®, the first stem cell product to be approved by the EMA. Giuseppe Chiericatti, general manager of Chiesi Spain, notes that “since Holoclar® is not reimbursed by the Spanish Health Service, we signed an agreement with HM Hospitals to make the drug available to patients in Spain. Signing agreements with the private sector will be an important part of making innovative therapies available to patients in the future.”

This, along with Chiesi’s work in public healthcare has generated “sustained, double digit growth in the last few years, not something to take for granted in Southern Europe. Moreover, we anticipate that we will exceed the EUR 100 million (USD 115 million) mark in 2019,” notes Chiericatti, who now has aspirations to focus on the launch of innovative rare disease products in Spain. To do this he is open to discussing innovative ways to increase the availability of rare disease therapies. This may be through novel risk sharing arrangements such as pay-per-performance.”

Spanish champion Esteve, also family-owned, is also prioritizing opportunities that may have slipped the attention of larger entities. New CEO Staffan Schüberg asserts that “If Esteve is to continue to grow, we must focus on smaller opportunities that Big Pharma may overlook.” Schüberg also notes the importance of strategic acquisitions for a company of Esteve’s size.

“We recognize that a strong pipeline requires multiple shots on goal, and we now recognize the need to complement our state-of-the-art R&D engine with a state-of-the-art business development chassis that can lead to more shots,” he states. “To do this, we are absolutely in the market for possible acquisitions and mergers with companies that represent a strong strategic fit for Esteve. We are looking for potential partners with mid- to late-stage pipelines that align with our core focus in neuroscience and gene therapy, solid growth projections and strong EBITDA, or could help us expand or complement our current European footprint.”

Giuseppe Chiericatti, general manager, Chiesi

Carlos Rus Palacios, general secretary, ASPE

Dr Juan Abarca Cidón, president, HM Hospitales

Carlos Rubió, executive president, Laboratorios Rubió
MEDTECH: THE RISE OF LOCAL CHAMPIONS

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Taboo Busting

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Alongside the usual multinational players such as Phillips, Siemens, Medtronic and B Braun, all of whom are present in
the Spanish medical device sector, Spain has seen a significant rise of local players acting both as distributors and as innovators of their own in-house designed products.

One such player is Cardiva, which “began life as a distributor, primarily for the US company Medtronic, focused only on northern Spain. In 1990, Cardiva made an agreement with a Scottish company and began distributing all over Spain,” explains Ignacio Vega, the company’s president. “During the 1990s, we realized that focusing solely on distribution would always be limiting to our growth aspirations, with the continual consolidation, mergers and acquisitions of smaller manufacturing companies making it a very unstable market. Therefore, we began to look at investing...

Spain’s ophthalmology market is Europe’s fifth largest but low levels of eyecare awareness among the general public and a constrained healthcare budget mean that new market entrants may find it difficult to navigate.

Ana Fernández, Spain country manager of French ophthalmologic specialist Laboratoires Théa, explains that “Generally speaking, there was a low awareness of eye health, retinal diseases and glaucoma in Spain – with the exception of dry eye – until 2012. Before that point, Spain’s national health system reimbursed all treatments for eye care totally. When someone had an issue with their eyes, they went directly to their doctor who referred them to a specialist. However, in 2012 artificial tears were de-reimbursed and it became an OTC market. Pharmacies started to play a larger role in the recommendation of dry eye products.”

Fernández continues, “Health Authorities take ophthalmology seriously but we, as an industry, also need to remember that they have serious budgetary constraints. There needs to be greater industry-government collaboration to find solutions... There needs to be a more holistic view, beyond the molecule itself.”

Théa, present in Spain since 1996 as the group’s first affiliate outside of its native France, has been able to find success in the Spanish market and Théa Spain now stands as the company’s third most significant global affiliate in terms of revenue.

Fernández ascribes this success to the company’s longstanding commitment to Spain and sole focus on the ophthalmologic niche. She posits that “We are competing with both big local players as well as the huge international companies. For these big companies, ophthalmology is a relatively small part of their business, but for us it is everything. This helps us make a difference due to our expertise and our passion for ophthalmology but also thanks to how seriously we take building partnerships with research and training programs within ophthalmology.”

in our own manufacturing facilities. We found a small family company in Malaga, southern Spain, which had been developing products for surgical use for J&J.”

This initial investment was followed by the acquisition of a manufacturing plant near Shanghai, which acts as the group’s main manufacturing hub, as well as a factory in Barcelona. With substantial revenue growth, Cardiva is now investing a large sum into the Malaga plant to match the company’s international aspirations. According to Vega, these “investments will double the production capacity of the plant. Each day we export more and more products, and this is our priority. We want to expand in many countries in order to minimize the risks inherent in focusing on only one country. Currently, between 35 and 40 percent of the Malaga plant’s production goes to exports, but our future goal is for this percentage to rise to 90 percent.”
These plant upgrades also fulfill another “key priority of being able to offer medical professionals a complete portfolio of products” expresses Carlos Ibares Sanz, Cardiva’s director of corporate negotiations. “In terms of manufacturing, we want to consolidate what we already produce as well as expanding capacity. With the upgrades to our Malaga facility, we are now able to manufacture Class III medical devices.” Ibares also believes that future growth will come from international expansion. “The next step is to look for partners in other countries that could develop as Cardiva has in Spain,” he opines. Furthermore, Cardiva sees R&D as a key step in this process, with the overriding long-term objective of wanting to be “disruptive with one of our own technologies!”

BEYOND THE FAMILY

Another local player to boom in recent years is the Barcelona-based Palex Group. The group, which had been family-run throughout its history, appointed an external CEO, Xavier Carbonell, in 2008 and revenues have since tripled, sitting at roughly EUR 150 million (USD 173 million) in 2018. This according to Carbonell, was triggered by a decision “around four years ago when the company was turning over around EUR 100 million (USD 115 million) annually. I was asked by the family to construct a business plan for the following five years, so I came up with two cases. The first was to continue on our current pathway, being a family-owned company. The second was a much more aggressive approach and was ultimately chosen, built around investment from a VC fund. At that time the Spanish market was filled with companies struggling financially. We could have let them fade out, but instead we decided to acquire these smaller entities and grow our network across Spain. Furthermore, we made acquisitions of larger groups that had their own portfolio that was different to ours. This not only allowed us to grow in size, but also increase the size of the product range that we offer to the medical community and to patients.”

Complete Cleanroom Solutions

Carlos Espina, managing director bio & pharma, COMSA Cleanroom Technology

One element of the bio and pharmaceutical value chain that almost all players involved in R&D or manufacturing require is cleanroom technology. With pricing pressures abounding, cleanroom service providers are increasingly having to bring a more complete package to the table to offer value for money.

One such specialist is COMSA Cleanroom Technology, the annual revenues of which skyrocketed from EUR 20 million (USD 23 million) in 2016 to EUR 45 million (USD 52 million) in 2018 thanks to a rollout of more consolidated cleanroom services. Carlos Espina, the company’s managing director explains that, “Under current market conditions the pharmaceutical industry is all about big value. This is what we are aiming to achieve with our expertise in that sector and, specifically, in blow fill seals processes.”

Espina outlines COMSA’s holistic approach to cleanroom solutions thusly: “We have a specialized R&D team that is centred around new technologies, specifically in heating, ventilation, and air conditioning (HVAC). That includes HVAC sterilization via peroxide as well as lean and maintenance systems. Our role is not only to bring the solution to partners when using HVAC, but also provide the required maintenance along the way and post-completion.”

He continues, “Our overriding goal is to be the main project contractor and manager; meaning a general contractor for civil works, black utilities and pharmaceutical installation for clean utilities. These services entail architecture, medicinal gases, purified water, HVAC and production equipment among others. In other words, we provide complete turnkey solutions for the pharmaceutical industry!”
Carbonell also highlights the success of a shift in Palex’s positioning towards becoming the exclusive distribution partner for companies without a footprint in Europe, such as the joint venture (JV) struck with JIMRO (Otsuka Medical Device Company). This JV according to Carbonell, “will over time begin to include JIMRO’s new technologies. We are currently distributing in the UK, Germany, France, the Nordics, Spain and Portugal, while in the meantime building relationships to soon move into Eastern Europe and other countries.”

Palex’s strong distribution footprint is, however, only the foundation for Carbonell’s true goal: developing products utilizing in-house R&D. To do this, Palex has its “own R&D department and business development team that is working to find innovative solutions. Though investing this money is one thing, the critical part is how we work, and this must be smart and targeted.” This has led to the realization that two areas must be targeted, “Firstly, neurovascular, and our knowledge from the cardiovascular sector will assist us in this. Secondly, robotics, which we believe has huge potential.” Carbonell will be looking to target the European and LATAM regions, as the company already “understands that from our distributor background the regulations in each market are vastly different. Therefore, we are working hard to find the perfect partners, and thus far we have made some encouraging progress.”

A WORLD-BEATING HEALTHCARE APPARATUS

Alongside Spain’s flourishing biotech and industrial fabric, the country’s stellar healthcare system also holds significant additional appeal for potential life sciences investors. Spanish healthcare is ranked as seventh globally by the WHO, beating out Japan, the Netherlands, the UK and the USA. Meanwhile, Spain rates as one of Europe’s best performers in terms of life expectancy, ranking fourth globally and second on the continent, with Madrid distinguished for possessing the highest life expectancy in Europe at 85.2 years!

That is not to imply, though, that the national health system does not face considerable sustainability question marks after years of budgetary constraints and rising demographic and epidemiological pressures. Health spending as a percentage of GDP has fallen below the symbolic line of six percent and more than 17 percent of the population is over 65 and aging while a massive 80 percent of the health system’s cost constitutes responding to chronic illness.

“The country was on a good trajectory until the global financial crisis and although the investment level started to recover after 2013, we have still not reached the pre-crisis levels. Capital public investment remains low and the obsolescence of systems remains high,” warns Juan Sanabria, general manager of the Iberian cluster of Philips Healthcare.

“Logically, the solution is to rethink healthcare provision in which patients can access all their treatment needs in the most efficient way possible. Naturally, we must increase the number of resources allocated to chronic disease and with regard to specialization and patient treatment, there will be a greater need to meet individual needs,” proposes Enrique Ruiz Escudero, minister of health for the Madrid community.

Interestingly, Spanish stakeholders have been at the forefront of trailblazing the concept of the “liquid hospital”, which envisions the virtual and physical expansion of healthcare provision beyond the parameters of the traditional centralized hospital structure. The aim is to leverage connectivity, telemedicine, the Internet of Things (IoT) along with social media to co-opt patients, families and society into the management of disease.

The model, being contemplated and trialed by a number of pioneering entities, “combines architectural advantages and clinical functionality thanks to an enlightened infrastructure design that takes into account health management and relates spaces to their surroundings, transcending the static building that quickly becomes obsolete and instead generating dynamic spaces, prepared to change their use, adapt and grow in a sustainable manner according to emergent socio-demographic needs,” notes Ángel Navarro, president of the science and health consultancy, Azierta.

“We are striving to re-conceptualize health management, a new area in which we offer expert consultancy in model designs, optimizing access to innovative products and technologies, whilst at the same time working to design new infrastructures related to health, such as dynamic hospitals and monographic units for patients,” explains Navarro. “Essentially, we are trying to integrate more technology into the services we provide, which is imperative if we are to continue delivering such strong results for our clients. The digital transformation of the healthcare sector is a trend we need to pay attention to, as this will revolutionize the entire value chain of health provision as well as the modus operandi of the pharma industry.”

Barcelona’s Sant Joan de Déu hospital, for instance, is working on the creation of a portal where patients and their families can gain access to health test results and access a broad range of telemedicine services without having to leave the home.

GE Healthcare, for its part, is experimenting with its very own concept of “hospital command & control center,” borrowing from other disciplines like the aviation sector. “The Command Centre strives to transform how care is delivered and organized. Utilizing artificial intelligence, it will provide a clear, instant, and real-time overview and help staff make quick and informed decisions on how to best manage patient care,” recounts the company’s CEO for Spain and Portugal, Luis Campo.
Now, more than ever, there is a blurring of the lines between pharma companies and digital health companies. But, at the same time, there is also a fundamental, unspoken divide between the two business models that are causing those blurred lines to clash more often than align.

This point was never clearer to me than in early January, when I did something a bit out-of-the-box for a trade publication that covers the pharma C-suite during the annual J.P. Morgan Healthcare Conference in San Francisco. I left J.P. Morgan for a day and attended the Digital Health Summit taking place as part of the Consumer Electronics Show (CES).

Gasp! Why would an outlet covering pharmaceutical executives leave arguably the biggest conference for that demographic to go to a technology show? Because, to understand the challenges of those we serve, we need to be in the trenches with them, if not one step ahead.

Both digital health and digital therapeutics are going to be top-of-mind issues going forward for any executive in the pharma, biotech, or biopharma fields. In fact, in our January issue, I reported that some pharma companies were going to be splitting their time between J.P. Morgan and CES (see bit.ly/2RhYtEd).

Fundamental differences
It really can be a confusing time for executives in the life sciences industry. Going from J.P. Morgan to the Digital Health Summit at CES, with less than 12 hours in between, the stark differences—and similarities—between the two camps were easily identifiable. Had that not happened, I don’t know if I would have felt such a culture shock between two spaces claiming to want the same outcome: Make a healthier population and cure diseases.

In reality, however, there is a fundamental difference keeping these two spaces running parallel to each other instead of merging closer together. A major reason digital health is so hard for pharma is because, if the big ideas of digital health actually deliver, it will help prevent some of the incidents that pharma is designed to treat.

“If this were a pill, we wouldn’t have an issue,” said Bruce D. Greenstein, executive VP, chief strategy and innovation officer for the LHC Group, and former chief technology officer for the US Department of Health and Human Services (HHS).

His remark came during a panel discussion at the Digital Health Summit, entitled “Boldly Going Where No Tech’s Gone Before,” and was referring to innovative health trends that tend to not to be covered by insurance.

Many similarities
This disconnect can grab headlines, as proven by the fact I am writing about it. But one of the benefits of attending both conferences in the same week was also being able to see the similarities between the two spaces.

While some say that future of the industry is driven by innovation, I believe the future of life sciences, including pharma and digital health, is going to be driven by open-minded leadership. Whether it was the CEO of a small digital therapeutics company at CES, or a multibillion-dollar, well-established pharma giant at J.P. Morgan, the numerous conversations I engaged in during that week last month all had a common theme. It was strong C-suite leaders who were not only passionate about what their companies were doing, but were naturally curious about the future of the industry, understood the various players in the life sciences world, and really wanted to make an impact.

These leaders represent the future C-suite life science executive. While they do have an area of expertise, they are also savvy in a variety of roles. They are former CFOs who are now CEOs. They are scientists who are also engineers with an MBA. They are pharma-trained business development folks who are running their third or fourth biotech startup, and know how to successfully build a bridge between the two segments of the industry.

Intrigued by these executives’ stories? I hope so, because these are just some of the interesting people who will be future guests on the Pharm Exec podcast and profiled in the pages of Pharm Exec throughout the year.
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