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VOLUME 35, NUMBER 4

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HBA 2015 WOMAN OF THE YEAR

Denice Torres

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The New Health: Navigating with Nash

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NOTHING IS AS DESTRUCTIVE TO B2B JOURNALISM as slaking the thirst for content from the same familiar well of sources. It is particularly harmful in healthcare, a sector composed of many separate parts, whose isolation is reinforced by the guild-like behavior of professional medical practice; a historically dependent and hugely uninformed patient population; and government regulations that reward narrow episodes of care rather than broader health outcomes. In fact, even after decades of progress in the use of drugs against diseases, in some circles it is still debatable as to whether our chosen business even qualifies as a health service.

The ongoing struggle to define the proper place of pharmaceuticals in healthcare is evident in the pages of this month's issue. We segue from the global obsession with compliance standards, in which the inducement to prescribe is seen as behavior fraught with serious ethical implications, to the cover feature on the 2015 HBA Woman of the Year, Denice Torres of J&J. Her steady rise in the executive ranks is due to a dedication to changing that negative perception by fostering public trust in the company's products: where the simple act of opening a bottle of pills is a seamless—and tension-free—act of individual consumer empowerment.

Pharm Exec is moving in the same direction, seeking ways to diversify our content through better connections with stakeholders in adjacent, non-traditional parts of the global health community. A vital driver of this effort is *Pharm Exec*'s Editorial Advisory Board (EAB), 31 experts representing nearly all segments of the modern healthcare enterprise as well as numerous geographies, from Russia to India to Canada as well as the US.

Photo: John Halpern

EAB members, seated (left to right): Kristen Spensieri; Sanjiv Sharma; Kenneth Kaitin: Joanna Breitstein: Dr. David Nash; William Looney; Dr. Graham Hughes; Michael Swanick **Standing (left to right):** Les Funtleyder; Michael Ringel; Murray Aitken; Mason Tenaglia; Bob Jansen; Rajesh Nair; Terry Hisey; Joseph Truitt; Terese Waldron; Peter Young; Rob Dhoble; Bernard Lachapelle; Frederic Boucheseiche; Don Creighton; Ian Wilcox; John Furey

This year's EAB meeting was held on Feb. 25, hosted by Dr. David Nash, Dean of the Thomas Jefferson University School of Population Health in Philadelphia, and a leading expert on this most externally driven, integrative approach to health management. Population health is founded on the assertion that 20% or less of an individual's well-being depends on the formal health system. Despite the vast amounts of money spent on acute care, where you live—your zip code—is a more reliable indicator of health status, along with family background, gender, and education, all of which tend to encourage reliance on lower cost preventive health behaviors.

Founded in 2009, the School's mission is to create leaders for the "no outcomes, no income" healthcare system taking root in the US, with an annual budget of $6 million that funds five separate masters degree programs for 300 students from 30 countries, many of whom are practicing physicians interested in managing ACOs and other emerging players in financing and delivery. The School also has an active research program, with support from key industry players like Janssen and Eli Lilly.

Nash and the EAB members underscored the need for more industry cooperation with the population health community around an evidence-for-outcomes research agenda. "In population health we have tremendous analytics capabilities. It's in the interest of the R&D industry to make better use of the data to structure how the next generation of health decision-makers approaches the allocation of increasingly scarce resources. If you don't, others will do it for you," Nash told the EAB.

For more on Nash and population health, refer to our cover profile in *Pharm Exec*'s March 2014 issue (pharmexec.com/population-health-call-community). Nash stands out as a restlessly inventive and colorful anomaly in a sector marked by gray shades of careful circumspection—and if you require proof, check out those socks in the group photo at left.

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On The Cover: Denice Torres, president of J&J's McNeil Consumer Healthcare unit, celebrates with her team (photo credit: John Halpern).

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Energy reform may be stealing the headlines in Mexico, but a rising regulatory authority, the beginnings of healthcare reform, and cost-competitive manufacturing are fueling future growth in the country's pharma industry—for domestic and global players alike.

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Poll data courtesy of online *Pharm Exec* readers between July 1 and July 30, 2014

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■ *@PharmExecutive What if patients are the center of the bullseye? Docs & payers can be the centers of outer circles?*

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Are Times A'Changing for Drug Marketing?

FDA is under pressure to moderate oversight of pharma advertising & promotion

Less restrictive rules on drug advertising and promotion may be emerging from FDA, as the agency responds to high court decisions questioning government actions that curb communications, particularly truthful statements. Radical shifts in the prescription drug market, moreover, are directing industry promotional efforts away from prescribers and toward informed payers that decide coverage based on broader outcomes data, as opposed to company advertising.

FDA officials have launched a high-level review of medical product marketing regulation to address pharma demands for reduced oversight of industry statements that are accurate, balanced, and not misleading —including discussions of off-label uses. The hope is that this will lead to greater flexibility in how companies convey risk information through new media and to new audiences.

Getting briefer

A sign of the times is FDA's recent publication of guidance on how to provide a "brief summary" of drug side effects and effectiveness in print ads to be more helpful to consumers. Although everyone has long quipped that the tiny-print package insert accompanying drug ads in newspapers and magazines is neither "brief" nor a "summary," it has taken the agency more than a decade to modify this requirement. The process has involved research studies on whether consumers actually read brief summaries (less than half), if detailed safety information is useful (not very), and which formats best convey important risk information (fairly simple ones).

The revised guidance actually discourages distribution of full prescribing information to consumers and "strongly recommends" that marketers adopt more patient-friendly formats and present a clearer and more useful summary of most pertinent information on the advertised product. The February guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM069984.pdf) was developed by the Office of Prescription Drug Promotion (OPDP) in the Center for Drug Evaluation and Research (CDER) and replaces one from 2004. It directs advertisers to use headings, larger fonts, and more white space to make prescribing information easier to read and recommends highlighting significant information such as boxed warnings, frequent adverse events, and key indications. There's even specifics on adopting clear language, such as "do not use" instead of "contraindication."

Newspapers and magazines may lose business because pharma companies will be able to run shorter ads, but medical journals still should see lengthy promotional pieces, as the abbreviated format is limited to consumer-directed communications; health professionals will continue to see the full PI.

FDA officials have launched a high-level review of medical product marketing regulation to address pharma demands for reduced oversight of industry statements that are accurate, balanced, and not misleading

This quest for clear, more useful drug information could carry over to direct-to-consumer broadcast advertising in the future. OPDP issued a notice a year ago seeking comments on options for modifying the lengthy risk information provided in TV drug commercials. The aim, similarly, is to make consumers more aware of most important safety issues for a medicine, and not muddy the picture with long lists of possible side effects. OPDP is testing various formats for "major statements" in DTC drug ads, though any policy change is years away.

Marketers asked OPDP staffers at the Drug Information Association (DIA) Marketing Pharmaceuticals conference in

Jill Wechsler is *Pharmaceutical Executive*'s Washington correspondent. She can be reached at jwechsler@advanstar.com.

February whether to start revising brief summaries as proposed in the new guidance—or wait 10 years for a final version. It's still unclear just what items advertisers can omit from a brief summary, largely because consults with OPDP reviewers on voluntary modifications in risk information often have yielded requests to add more specifics to these statements. But OPDP regulatory counsel Julie Chronis advised industry to start implementation now, even though some of the details may change. Comments are due May 10.

Social media struggles

Last year OPDP also issued highly anticipated guidances on the appropriate use of Internet websites to convey information on prescription drugs. One advisory addresses communicating about drugs in limited spaces, such as 140-character "tweets" with little room for risk information. Another discusses how companies may correct erroneous information about a drug posted by third parties. OPDP also advised companies not to submit every new Internet posting for agency review, but to provide periodic updates on online communications activity. Further guidance is expected on how marketers can convey risk information through "links" to additional sites, a common Internet practice but one that FDA has found inadequate for ensuring fair balance about drug communications.

While FDA says it aims for more clarity and flexibility, marketers complain that the new policies are impractical, confusing and overly restrictive. If a pharma company wants to correct a third-party message, for example, that may mean correcting all postings on a topic—or face "cherry picking" charges from OPDP. Some companies thus are deciding not to correct anything, even though that approach may not be best for public health, commented attorney Scott Liebman at last month's IBC Pharmaceutical Compliance Congress.

In addition to revising these guidances to further clarify how companies may use social media more effectively, industry is anxious for FDA to lay out a more practical approach for providing economic information on medical products to "educated" parties, such as formulary committees, insurers, and payers. FDA has promised guidance for marketers on conveying healthcare economic information in promotional materials, an important topic that has been mired in dispute for decades.

It's not surprising, though, that pharma companies are nervous about modifying brief summaries and experimenting with Internet postings, as inadequate risk information continues to be the main compliance issue cited in OPDP enforcement letters. There have been fewer OPDP enforcement actions in the last year—only 10 untitled letters in 2014, compared to 26 in 2013—but overstatement of benefits compared to side effects remains the top violation.

OPDP director Tom Abrams suggested at the DIA conference that the decline in enforcement action may arise from FDA success in gaining voluntary correction of noncompliant materials before stronger enforcement action is needed. Despite such gains, industry critics continue to contest moves to liberalize FDA pharma marketing rules. Public Citizen's Sidney Wolfe recently broadcast strong opposition to the agency's proposal to permit marketers to hand out peer-reviewed journal articles to doctors. Wolfe cited thousands of individual comments filed with FDA that similarly reject this revised policy and warned that pharma journal handouts would undermine FDA's authority, mislead customers, and endanger patients. Evidently, not everyone seeks moderation in the pharma promotion area. PE

What's comparable?

The emergence of biosimilars raises a number policy issues for marketers, including questions about what evidence FDA will require to support claims of superiority or comparability for products approved as similar, but not necessarily interchangeable. Unlike conventional generic drugs, biosimilars are developed and approved as "highly similar" to a reference drug, but not completely the same, noted AbbVie vice president Tracey Rockney at the recent Drug Information Association (DIA) Marketing Pharmaceuticals conference. She questioned whether OPDP will permit claims such as "works the same" or "just as safe," particularly for a biosimilar approved for some, but not all, brand indications. Another tricky issue is how marketers should substantiate economic claims, such as "more affordable."

Where clinical superiority is somewhat hazy, biosimilars makers may promote quality manufacturing capabilities and product stability and reliability. At the same time, brand marketers that disparage the safety and efficacy of approved biosimilars may hit OPDP's radar screen. FDA guidances on biosimilar naming and on demonstrating interchangeability should help clarify these issues.

A sponsored advertorial.

Are You Asking Your CRO the Most Important Questions?

Sara Davis, Senior Vice President of Global Business Development, Theorem Clinical Research

By Sara Davis, Senior Vice President of Global Business Development, Theorem Clinical Research

Decades of experience. Thousands of employees. Dozens of feet on the ground in dozens of countries. Hundreds of studies conducted in every major therapeutic area. Sound familiar?

Most CROs take a book-by-its-cover approach to presenting their capabilities, just as prospective clients do when assessing them. Budgets aside, when it comes to relevant experience, size and global reach, it is often easy to rely on numbers presented rather than digging deeper.

The above are standard buying criteria, and while these things are important in terms of explaining what a CRO has done, what is often overlooked, and what is arguably more meaningful to the success (or failure) of your study, is the team that is assigned and what it's currently capable of executing. Do the team members possess the necessary experience? Are they going to be as passionate about the outcome of your study as you are? While a CRO may have executed a major trial similar to yours, are the same people that executed that trial still on the team? Is the executive leadership team that constitutes the decades of experience and therapeutic area expertise going to be actively involved in, let alone aware of, your study? These questions and the ones that follow are important to ask when selecting a CRO.

Will My Project Be a Priority?

Applied expertise, flexibility and dedication drive successful trials, and while many CROs make these traits part of their business philosophy, they fail to put that philosophy into practice. For example, if you don't award a minimum dollar amount each year, your projects may not

receive the same level or extent of attention as larger projects or preferred provider relationships that may be in place, which could include your competitors. At Theorem, unlike many other CROs, the money you spend isn't what makes your study a priority. Every project team at Theorem is incentivized based on high-quality deliverables and client satisfaction.

Does the CRO Truly Have the Expertise to Understand My Unique Requirements?

To compound the problem of prioritization, there's the matter of allocating experience. Experience doesn't come in bulk. Consider the misconception that medical device trials are essentially drug trials with less rigorous processes. Many CROs follow the same processes and involve the same leadership on medical device projects as they do for pharmaceutical projects, only to discover that when you drill down into medical device trials, they are radically different. Specialized expertise can't be replicated or generalized, especially in the context of combination product development (e.g., drug/drug, drug/device, biologic/device, diagnostic/drug, diagnostic/device) whereby a CRO must apply cross-functional expertise.

Can the Technologies Offered Fit My Unique Study and Company Needs?

As the research community embraces individualized approaches to medicine and targets new sources of patient and disease information, it's generating more data than ever. In turn, trials are more complex, and so are the technologies used to collect, manage and analyze data. Today, the industry is no longer limited by tools, but rather by the ability to combine, deploy and manage these complex tools in ways that simplify research and drive innovation. Any CRO can implement an off-the-shelf technology, but for today's complex trials, that's not enough. To properly explore and interpret data, technologies must be tailored to the projects they support and the people facilitating those projects. Does your CRO have the ability to customize technologies to meet your unique study and program needs?

Does Global Reach Mean Global Expertise?

Many sponsors require a CRO that can conduct their study globally; however, they fail to assess true global expertise. Having a mailing address is not equivalent to having true access to the country or the region-specific cultural and regulatory intelligence necessary to effectively execute a trial. What are the CRO's study team relationships like with the sites in the region? What are the CRO's relationships with regulators in countries where your trial will be active? Many CROs can offer global reach; however, the global expertise to effectively execute trials in the countries of interest is another matter.

Once you go beyond high-level numbers, accolades and basic abilities, you will find that what really matter are the people who will work on your studies and the expertise, attention and dedication they apply to make your work as important to them as it is to you. When you're assessing research partners for your next trial, ask yourself, **what's really important?**

Putting Off Off-label Decisions in Europe

The EU's proposed new study on off-label prescribing is just another way of kicking the subject into the long grass

When in doubt, commission a study. This well-known tactic has come to the rescue of the European Union (EU) once again in the face of renewed controversy over off-label prescribing of medicines. EU officials are now pondering who they should nominate to provide a study on the subject, and a decision is expected shortly. The envisioned starting date for the study is the first quarter of 2015 and it is anticipated that the study will be finalized this year. All of which provides the EU with a perfect excuse for doing nothing in the interim about off-label prescribing.

On the offensive

That isn't going to satisfy the research-based industry. Companies with innovative products have been fulminating for years about the risk—risks to public health, they like to say, although they also add, *sotto voce*, risks to profits. They went on the offensive early this year with a joint demand to the European Commission for urgent action against Italy, where *voce* has not been at all *sotto* in an epic clash that has developed over health ministry recommendations that a cheap cancer drug should be used instead of an expensive eye drug. The product at the centre of the complaint is Roche's cancer medicine *Avastin*, which the Italian health ministry has been reimbursing since last summer for use as an eye treatment, in preference to the more expensive *Lucentis* from Novartis. Italy is ignoring EU medicines rules and its action "undermines key elements of the EU pharmaceutical regime, in particular the marketing authorization system," says the complaint, which has been put together by the European Federation of Pharmaceutical Industries and Associations, EuropaBio representing biopharmaceuticals, and EUCOPE—the European Confederation of Pharmaceutical Entrepreneurs, which represents a number of mid-sized innovative pharmaceutical companies.

That isn't going to satisfy the research-based industry. Companies with innovative products have been fulminating for years about the risks—risks to public health, they like to say, although they also add, sotto voce, risks to profits

They argue that the Italian measures, introduced just over a year ago, "are based on budgetary considerations that should never overrule the protection of public health." They point to a procedure for listing certain off-label uses of medicines that can then be reimbursed, based on, among other criteria, cost-control considerations. And they cite a judgement by the EU's highest court that prohibits member states from reverting to off-label use as a cost-containment measure in cases where approved alternatives exist. But the Italian courts have taken a different view: just over a year ago, they fined the two companies more than $200 million for collusion in seeking to protect profits from *Lucentis* by opposing off-label prescribing of Avastin. The Italian approach is strongly defended by European consumers, who instigated the Italian court case; national health authorities should intervene to protect overriding public health interests, they insist—including protecting the public purse.

The industry call for action has wider implications than merely putting a stop to leaks in Italy's application of EU drug rules. "Similar practices occur more and more in other member states, through therapeutic recommendations or by setting budgets for specific medical procedures at levels that *de facto* impose off-label use of medicines or the use of unapproved medicines instead of authorized products," says the complaint. If this is allowed to go on unchecked, research and develop-

Reflector is *Pharmaceutical Executive*'s correspondent in Brussels.

ment of new medicines will be discouraged. EFPIA already publicly criticized an announcement by the French government that it intended to enlarge the use of off-label drugs for economic reasons. Last July, the industry association said the plan was in effect creating "secondary national marketing authorizations" and "could potentially put patients at risk." And only weeks ago, a Spanish official proudly displayed to European colleagues in the latest EU committee on drugs, known as STAMP, the rules in Spain that allow off-label use.

Divisive issue

This is just some of the background to the impending study on off-label use. But the confrontation is not just between a couple of rogue member states (backed by consumers) and the industry. There is hardly any agreement at all among European regulators on the subject. Or indeed between EU institutions. More than a year ago, the European Parliament adopted a resolution on patient safety that called for specific action regarding the off-label use of medicines. It urged the European Medicines Agency (EMA) to "draw up a list of off-label medicines, which are used in spite of there being an approved alternative," and said it should "develop guidelines on the off-label use of medicines, on the basis of medical need, and taking account of patient protection."

The European Commission, which is responsible for seeing that EU laws are complied with (and for proposing new laws where they are needed), responded to the Parliament with caution: "Although EU legislation regulates marketing authorizations of medicinal products, it does not specifically regulate the off-label use of medicinal products," it pointed out. So "the issue of off-label use of medicinal products is complex and deserves consideration"—and while it grudgingly acknowledged that EMA "could be an important player," it warned that an EMA list of medicines used off-label might not be representative. "Not all member states have the same approved medicinal products on their market," the Commission remarked, and some countries have already developed their own recommendations and guidelines for off-label use. Consequently, the call for action by EMA "would be premature."

A viable solution?

So a study is a much better idea. It solves nothing, but it satisfactorily puts off any obligation to act until well after the study has delivered its findings. For a Commission that is hesitant to provoke further resistance in the health arena from member states (who have already shot down two recent Commission proposals—one on information to patients, and the other on drug pricing and reimbursement mechanisms), a study is a very respectable solution. All the more so since it will have a wide scope.

It will look from the scientific perspective at public health aspects, and, in particular, patient safety. But the study will also look at the legal questions relating to the regulatory framework. It will gather information—eminently safe as an initiative. The study should "systematically consult the members state authorities and stakeholders (patients, healthcare professionals, and industry)" on current practices, the drivers for off-label use (essentially, the availability of duly authorized products, and their cost), and measures in place to ensure patient safety. And the information collected will serve "to identify if there is a need for coordination at EU level and, if so, possibly, to what extent," according to a summary of the preparatory reflections among senior EU officials. As a double safety-catch on having to take action, the preparations explicitly noted that "We do not intend to be conclusive at this stage regarding the definition of off-label use," and the consultant chosen will be expected to extend or modify the working definition. That should all keep everyone busy until the end of this year—obviating any stress among officials over the ongoing controversy.

Don't complain to us

The current Commission position is comfortably hands-off on the question. EU legislation on medicines does not regulate off-label use. "It is the marketing authorization that defines the approved indications," say Commission officials. "Any departure from those terms will remain, in most member states, the responsibility of the prescribing physician." In other words, don't come to us. If you've got a problem, talk to the member states. And if member states have a problem, then they will have to talk to doctors. But leave us alone. We've started a study. What else do you want? PE

Photos: John Halpern

Denice Torres, president of Johnson & Johnson's McNeil Consumer Healthcare division, celebrates with her team.

J&J's Real Deal

To Healthcare Businesswomen's Association 2015 Woman of the Year, Denice Torres, doing right starts with finding—and being—yourself

By Kathleen Raven

At her Catholic high school graduation, Denice Torres sat near the back of the auditorium, separated from peers who received high academic honors. The Indiana native must have struck an image: sandy-brown hair, athletic build, light hazel eyes, and a demeanor bristling with ambition. As she listened to speakers onstage in the spotlight, Torres remembers thinking, *We'll see. There's more waiting for me*. That refrain from her 18-year-old self still echoes in her mind today.

Modest roots

Growing up in the grimy steelmaking citadel of Gary, the middle child of a Polish mother and Hispanic father, Torres quickly learned nothing would be handed to her. In an upbringing she describes as lower-middle class, fear mixed with hard work kept Torres, her older sister, and younger brother, focused on the world beyond their neighborhood. A huge industrial plant sprawled through the lot across from her family's three-bedroom house, while abutting their property stood the Careful Car Wash.

Torres' father, Joe, worked in the US Steel mills. After retiring, he became president of Gary's public school system,

the first Hispanic person to do so, which, she points out, was no easy achievement at the time. After raising three children, Torres' mother, Joan, wanted to do something for herself. Torres compares her mother to Maude Findlay, the namesake character of a Norman Lear television sitcom from the 1970s, who was an outspoken liberal and women's rights advocate.

Joan got a job performing non-clinical tasks at the local hospital in Gary while earning her nursing degree at night. After graduation, she became one of the first certified school nurse practitioners in Indiana, another milestone for the Torres family. Joan spent a career serving disadvantaged kids in Gary's inner city schools. Besides her mother, Torres remembers her maternal grandmother, Genevieve, as a strong female role model. With only an eighth-grade education, Genevieve climbed the ranks to become assistant manager of a local bank.

Both parents instilled in Torres a sense of duty and service to community. Even with a strict focus on education, humor imbued the Torres family. Torres remembers mariachi music blaring at her paternal grandmother's house, where fresh tortillas were often fried on the griddle. At her maternal uncle's house, she heard accordion music and family stories. Dancing happened spontaneously and often.

Within this upbringing, sports played a major role for the young Torres. "There was no *Harvard Business Review* at that time, and so my strong female role models were women in sports," she says. By the time she was a junior in high school, she'd set her sights on a basketball scholarship and possible coaching career. Torres also continued to test her stand-up comic skills on the toughest audience—her family.

Making light

Humor has often been the refrain in her role as president of Johnson & Johnson's McNeil Consumer Healthcare division in Fort Washington, PA. "I'm very funny, I have to say," Torres says, in her characteristic deadpan manner. In high school, Torres was voted most athletic and funniest.

She earned a basketball scholarship to play at Saint Joseph's College in Rensselaer and played freshman year before blowing out her knee. She then transferred to Ball State University in Muncie. But Torres is grateful for the way things played out because it set her on a fast-moving path toward success.

"Without discomfort—and listening to that discomfort—in our lives, we tend not to change."

With extra time in her schedule, she enrolled in a psychology course and immediately fell for the subject. She changed majors and began soaking up lessons on human behavior and emotion she would use decades later in managing people and teams.

During her junior year of college, Torres visited a VA mental hospital as part of a class project. "It was the first time I was exposed to extreme mental illness," she says. Torres enjoyed figuring out how people respond in different situations, but a career as a psychologist did not kindle her passion. Since she was brought up to value education and hard work, she turned to a career that required both: law.

"I still remember opening that letter from Indiana University's Maurer School of Law," she says. The university awarded her a full scholarship. The analytical aspects of law captivated Torres and some of her most memorable academic studies happened while working together with her peers.

After graduation, she joined a Michigan law firm specializing in worker's compensation and medical malpractice. Over time, Torres realized that "the nature of law, and being a lawyer, means inherent conflict." For the former point guard basketball player, who valued playing and winning as teams, the individualistic environment in law did not feel like the best fit. At the same time, Torres noticed her favorite cases involved those with medical issues or components. She tucked this revelation away.

Stretch—even if it hurts

By this time, Torres was in her late 20s, and felt uneasy that she had not settled into a career. "But I also realized how much being uncomfortable can prompt us to do positive things. Without discomfort—and listening to that discomfort—in our lives, we tend not to change," Torres says.

Torres decided to answer a newspaper job advertisement as an account executive for a marketing and advertising agency. Even without marketing experience, the firm hired her immediately. "From Day One, I saw this group of creative, passionate, perfectionist people, working together as a team to give the best customer service, and I thought, 'This is me,'" Torres says. In her spare time she read copious amounts of marketing and research books and articles.

But something was still missing. Torres wanted her credentials to match her passion. She applied for University of Michigan's MBA program—one of the most competitive in the country at the time—and got in. As a 28-year-old business school student, Torres knew she'd found her niche.

She applied for a summer internship with Eli Lilly's Indiana headquarters and was assigned to help promote the company's then brand-new drug *Prozac* (fluoxetine). Lilly offered her a job in product planning and development at the end of the internship. One year later, she became a sales representative for *Prozac* and *Ceclor*. She quickly learned how she could differentiate herself from all other sales reps who came through clinic doors (and who were not always welcomed). "I started making personal connections with the receptionists. Instead of being the Ceclor rep, I became

the person with the cute niece who was just born," Torres says.

Connecting with Clark

Following her time on the sales front lines, she was promoted to market research manager within special projects. That is where she met Allen Clark, her first mentor and person who would have the biggest impact on her professional life. Clark directed Lilly's North American operations at the time and took Torres under his wing. The 37-year-old Torres was sometimes intimidated by the towering 6'3 Clark, who talked bluntly in his native Scottish brogue. "He was tough on me, but he believed in me," Torres says.

A turning point in her career arrived unceremoniously one afternoon just before Clark headed into a meeting to announce a new incoming director. "I remember he caught me in the hallway, pulled me aside, and said, 'I'm promoting you to director of marketing studies—now come stand next to me when I make the announcement,'" she recalls. Torres spent 18 months in that role and oversaw a reorganization of the department. In the process, she learned about re-engineering business processes and change management.

Satisfied with her work, Clark promoted Torres again, this time to direct the sales and marketing department of human growth hormone products. In her initial meetings, Torres stayed quiet on the sidelines. Clark stopped her one day in the office and sternly told her that she had been promoted so she would speak her mind and share ideas with the other directors at the table, who at the time were all male. "I felt free because he believed in me," Torres says.

Clark, like Torres, believed humor to be an important part of the workplace. He often injected chuckle-worthy mantras into conversation, such as, "When it's all said and done, there's more said than done," Torres remembers.

With her self-confidence flourishing, Clark then tasked Torres with turning around Lilly's failed osteoporosis prevention drug at the time. To set her team up for success, Torres compared the processes of revamping, marketing, and selling the drug with summiting a mountain. She realized metaphors like this could help a team stay goal-oriented and keep track of progress and what still needed to be done. From there Torres moved on to executive director of Lilly's global operations, primarily for *Zyprexa* (olanzapine), a franchise then worth $5 billion. She enjoyed the challenge of creating clinical and commercialization plans, but missed working with profit and loss on the business side. Underneath it all, Torres missed something else in her life, too: the self-acceptance required to be her authentic, whole person.

"I developed this empathy for people going through challenges at work. It is important to support people in their greatest time of need."

Climbing her mountain

Torres signed up for a seven-day Outward Bounds backpacking trip in California's Sierra Nevada. At the start of the expedition, she and others received fully-loaded 60-pound backpacks. Throughout the trip, they learned how to empty not only their physical packs, but also emotional baggage. "I was really hurting on that trip," Torres says. "I was overwhelmed by the beauty of the mountains and realized I had to find a way to be true to myself." A couple years later, Torres took the first steps of opening up to her colleagues. Before a communal work event, a colleague asked Torres if her partner, Kim, would also be attending. Torres explained that Kim had to work; it was one of the earliest times Torres talked openly in her professional environment about being gay.

Torres did not know that all of her toughness, hard work and grit would be rigorously tested in 2000 when her daughter, Sierra, was born. Sierra was born at 30 weeks of gestation—about two months too early. She weighed two pounds and 10 ounces. Torres and her partner endured a harrowing three weeks while Sierra stayed in the neonatal intensive care unit. "The person I am today has so much to do with what happened to me during that time period. It changed me forever," Torres says. "Either this was going to be the worst thing that had ever happened, or this thing of gratitude," she says. Bit by bit, doctors solemnly relayed grim updates to the parents. Sierra had cerebral palsy, hearing loss, and epilepsy. She would be confined to a wheelchair for life. "I just wanted to be this girl's mommy," Torres says. Finally, she took Sierra home. "I remember the first time I went to get diapers," Torres recalls. "I was strutting down the aisle like John Travolta because I could buy diapers for my girl."

When Torres returned to work, things had changed. Not everyone understood the need for her extended absence and the magnitude of what she had endured. "I developed this empathy for people going through challenges at work," she says. The experience taught her that a company is truly the sum of its people. "It is important to support people in their greatest time of need," Torres says.

First in the line of fire

In 2004, Torres hired on with Ortho McNeil Neurologics as vice president of marketing. She once again began her fast ascent through positions of increasingly demanding responsibility and leadership, and was brought in as president of J&J's McNeil Consumer Healthcare division in April 2011.

At the time, J&J was hurting from product recalls and would soon enter a consent decree with the FDA over its children's *Tylenol*, regular *Tylenol* and other OTC products. J&J pulled *Tylenol* products from the market at the first sign of trouble during this time, Torres

points out. From a safety standpoint, it was the right thing to do, she says. Early in her career at McNeil, Torres decided she would put certain processes in place so that *Tylenol* would emerge a stronger and better brand and product. "If you look at previous situations, like the cyanide *Tylenol* scares of the 1980s, you can see that innovations like the first safety seals on products came from that time period."

Torres regularly evokes the J&J credo, which includes Do the right thing and Keep your promises. "When I came into this role four years ago, I realized that we had to get back to our roots," she says. "Our mission is to deliver premium healthcare solutions with an unparalleled healthcare experience."

Early on in her role at McNeil, in an unorthodox style typical for her, Torres visited pharmacies and drug stores to hang out in the OTC medications aisle to observe customers. She remembers watching an older couple compare bottles and flip labels back and forth. After some time, the couple finally went to check out. But, Torres says, they eventually came back to the aisle because they were still unsure. "That always stuck with me," Torres says. She often explains to her team what the average person in the U.S. earns per year and what the same person spends on healthcare. Even an OTC drug that costs $8 is a big purchase for many people, Torres points out. "We have to differentiate ourselves by making the experience as near-perfect for them as possible," she says. This starts with the packaging on the outside, the instructions inside the packaging, the pills, the bottle, and opening the bottle itself. "After a purchase, I want consumers to say, 'I didn't expect that—that delighted me,'" Torres says.

Test two: Tylenol

Tylenol is one of J&J's most recognizable brands, but also one that has had to endure multiple crisis communication situations and quality control challenges, starting with the initial cyanide

Torres' leadership has been integral to the turnaround of Tylenol.

poisonings in the 1980s. In 2012, McNeil recalled nearly 600,000 bottles of infant *Tylenol* due to uneven dosing that resulted in too much or too little active ingredients. In 2009, two years before Torres' arrival, McNeil recalled some *Tylenol* brands after a wood-treatment chemical showed up in the medicine, causing nausea, vomiting, and diarrhea. During her first two years, Torres spent time restructuring and rebuilding "in the basement" with foundational aspects of the products. She worked on turning around processes and capabilities within the company. "This work is not sexy," Torres says. But the work cannot be shortchanged "because the strength of the foundation will be the strength of the house," Torres says.

Alex Gorsky, J&J's CEO and chairman, has observed her financial acumen and bold leadership style for many years. "Denice takes a 360-degree view when it comes to assessing and making business decisions," Gorsky says, adding that the best leaders "bring unique perspectives, courage, and a tremendous amount of compassion for people. That's Denice."

As part of the Tylenol turnaround, Torres saw a need for more frequent communication throughout her team of nearly 1,000 directors, managers, and staff. So she started a twice-weekly group meeting called Fireside Chats in which she would meet with different departments. She also started a biweekly town hall meeting event in the building's auditorium open to all employees, who could share their thoughts and ideas, and hear priority updates from Torres. Torres visits the manufacturing plants on the McNeil campus herself. She asks the managers to take her on a "Points of Pain" tour so she can know what changes need to happen where and when.

"Denice will always tell the truth—she is all about straight talk," says Natasha Zuyev, vice president, consent decree, McNeil Consumer Healthcare. "She helped my team reach our goals by creating a collaborative and caring environment and prioritizing consent decree work above everything else."

Torres says she taps into psychology lessons by regularly checking in with her team to know where they stand on the emotional journey that parallels a product turnaround. She tells them what to expect during the next stage and how people might deal with frustrations. "Denice has led McNeil Consumer Healthcare through transformational change with exceptional results," says Peter Fasolo, vice president, global human resources, J&J. "She brings an unwavering commitment to authentic leadership and is a role model for proper work-life balance."

When asked if *Tylenol* products have made a complete recovery, Torres hesitates. "They are doing very well, but I would not say they have recovered completely," she says. The pediatric OTC share has significantly increased and will likely fully recover, she adds. J&J, in her mind, remains one of the strongest global pharmaceutical companies. Worldwide consumer sales were $14.5 billion in 2014, Torres points out. The company had global sales of $74.3 billion in 2014, an increase of 4% over the previous year, according to a J&J spokesperson.

Be yourself

If Torres had to name only one passion, it would be providing support for and advocating on behalf of women to take on more leadership roles in the healthcare

industry. The message may be heard often, but it's true, women must be their authentic, total selves, she says. "I know what it was like when I was trying to be another person," Torres explains. She encourages employees to wear whatever they wish at work—whether it's jeans or a suit—because people must feel comfortable when they are working.

J&J does a tremendous job of hiring a diverse workforce and reflects the general population make-up better than most Fortune 100 companies, Torres says. But until more women are in leadership positions, the need for female executives must be prioritized and improved upon, she adds. Women must embrace the fact that they may feel insecure at times—but everyone is insecure, Torres explains. The notion that no one is perfect, and no one needs to be, should be communicated more often to women in the workplace, she adds. "Diversity is ideas, ideas are innovation, and innovation is what makes a company successful," Torres says.

"Denice's authenticity, transparency, and emphasis on fostering collaboration and mutual accountability for outcomes create an environment where people feel stretched and supported at the same time—and the business results follow," says Sandi Peterson, group worldwide chairman, J&J "She leads with energy and clarity of purpose in every situation and has a real talent for connecting with people at all levels of the organization. She has served as a mentor and a sponsor to many people at J&J, and has had a wonderful impact on many careers."

When she looks back on her career, Torres wants to leave a legacy marked by helping others be their very best self—from self-acceptance to self-celebration. "I am resolute in the belief that by being bold and helping others realize their potential, amazing things happen for everyone," she says. PE

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Women in the Workplace:

No management issue in life sciences is more important than building and retaining a diverse global talent base—demographics alone prove that this goal is unobtainable without the increased participation of women. As the Healthcare Businesswomen's Association (HBA) announces its latest choice for its Women of the Year award, *Pharm Exec* Editor-in-Chief William Looney sat down with Dr. Claudia Graeve, who leads the HBA's sole international chapter in Europe, on improving the prospects for female managers in a region that is surprisingly hesitant about embracing a world of business without boundaries—roots, of both the geographic and cultural kind, still run deep.

Dr. Claudia Graeve

Graeve, a scientist by training, signed on to the HBA network in 2010, starting as a member of the chapter's Marketing Committee, then serving as chapter vice president before taking on the top spot last year. Graeve's role puts her in charge of the overall strategic direction of the organization in Europe, complementing her day job as vice president at Health Advances, a Boston, MA-based life science strategy consulting firm, where she holds responsibility for the European Practice.

"My interest in the industry dates back to when I was only 14; I learned then for the first time I would need to push twice as hard as my brother to find success in this field," Graeve tells *Pharm Exec*. "I eventually obtained a masters in science and PhD in chemistry, at every stage having to work against the stereotype that women were not good in the exacting technical disciplines of math and science." What helped her prevail was the broader exposure she found through her father's work as an international executive, which allowed her to experience living in different countries outside her native Germany.

Pharm Exec: HBA is often assumed to be a "US-centric" organization. Can you highlight the role that HBA now plays in Europe—how deep are your roots in this, the world's single largest market for health care?

Graeve: Europe is one of 15 local chapters of the HBA, and the only one based outside the US. We have logged steady growth since the chapter was founded in 2007, and our membership now exceeds 300 women executives representing the various parts of the European Healthcare arena, including multi-national pharmaceutical and medical device companies, CROs, communication agencies, and start-ups shaping the future of healthcare technology. The best way to describe us is as a "chapter of chapters." Everyone who knows Europe recognizes the historical—and continuing—importance of national interests, and that sentiment is reflected in the way our chapter operates. The strategy is to offer members the HBA's global service framework coupled with a more focused, "hands on" local approach. Within the European chapter there are no less than nine active country groups: two in Switzerland, in Basel and Geneva/Lausanne; two in France, in Paris and Lyon; two more in Germany, in Berlin and Frankfurt; the others are located in London, Milan, and Dublin. Our Dublin and our Geneva/Lausanne groups are new and growing quickly due to strong interest in HBA activities among many of the CRO/CMO operations based in Dublin and due to the dense network of life science companies in the Lake Geneva region.

So overall, although HBA Europe clearly does not yet have the awareness HBA has in the US, we are a lively and thriving community, bringing together women (and men) from a variety of different countries and backgrounds. We are growing strongly and our volunteers are working across national and continental borders to create a solid common ground for members.

Pharm Exec: How do you strive for that distinctive approach in raising the profile of women in healthcare?

Graeve: The chapter's programs reflect Europe's geographic and cultural diversity. Although there are common challenges, the issues facing women executives in healthcare differ from

A View from Europe

country to country. For example, there is no core consensus throughout Europe on the meaning of "gender equality." From a purely legislative or regulatory standpoint, Sweden has one view, the UK has another, while basic cultural values diverge among the Nordics, the Anglo-Saxon countries, France, and southern Europe. I am German by background and I am well aware that rank-and-file support for women having their own career is not so strong in Germany as one might presume from abroad.

There is a lot of work still to be done in Europe to change attitudes beyond the law itself. This is why our activities emphasize networking and reaching out to those stakeholders who can help us put a human face on the value of workplace diversity.

Pharm Exec: Do you see real contrasts between the US and Europe with regard to the pace of progress on workplace issues affecting female executives?

Graeve: The US continues to exert strong influence on trends in Europe, if only because many of the practical aspects of workplace engagement started there. The big US-based global players in pharma took up female executive empowerment early on, in no small part because the HBA was founded in the industry's base in New Jersey back in 1979. That involvement by the US multinationals quickly took on a global dimension, which means that US corporate initiatives to promote women in management are extended to include the European operations and alignment initiatives are fueled to deliver a global approach to the topic.

This, in turn, has reinforced the competitive desires of the major European-based pharma companies to keep pace. Many, especially large, players in the industry in Europe now offer internal leadership training geared to their women employees as well as mentoring opportunities, which are often benchmarked against the competition. Quintiles, for example, conducts an annual survey of its performance on management that it rates against others in the CRO community and then uses to develop action plans for each of its local businesses. We are also seeing in Europe the extension of our agenda in corporate management performance reviews, including those of the most senior male executives. I suggest that has happened largely as a consequence of demands from corporate HQ for diversity programs that are globally aligned.

Pharm Exec: What are the European chapter's key program priorities for 2015 and beyond?

Graeve: The overriding objective is to keep growing the membership and to attract even greater attention to our cause. We recognize that women benefit from tailored support to make most of their career opportunities and we aim to act as a catalyst for personal and professional growth. It is the vision of a better future to which healthcare can contribute that inspires and uplifts us as women in this industry. It is an opportunity to share, to give and to co-create that we want to put at the disposal of our members.

How do we plan to do it? Through the three key pillars of our program offering. These consist of training opportunities in leadership and business thinking through our events; leadership development opportunities through volunteering; and a one-on-one mentoring program to fuel personal development. Our chapter provides access to an unparalleled network of women from different areas, different countries and different professional experiences and we plan to foster this diversity and grow the network further this year and in the years to come.

In 2014, we hosted 41 information, strategy and networking events, a fundamental pillar of our offering, as well as a pan-European summit, in Eschborn, Germany, that we co-hosted with EY, the global professional services firm.

This year's summit will convene in Amsterdam at the end of October and will center on managing global teams. This is an area that we are well experienced in, since our own Chapter Board is located all over Europe, not only in our nine locations. It works closely with the global HBA community to manage the local offering.

Our 2015 goal is to increase local events to 50 high quality events—an average of one per week, on topics that will drive a "leadership in practice" agenda, with the overall aim of advancing each member's career development, in a safe setting that allows for the sharing of experiences to help women" stretch" and raise their game in an increasingly competitive regional market for healthcare talent. We will also be relying more on webinars and other interactive online networking platforms to supplement face-to-face contacts. In line with these activities, we will continue with our cross-country mentoring program, a three-year-old program we have implemented across Europe to allow potential mentors and mentees from different organizations to apply online and where we facilitate the right match.

Though we intend to remain close to global flagship companies here in Europe, we are also reaching out to the mid-size pharma community, biotech, and service organizations like CROs. I personally believe there is significant potential in facilitating useful knowledge transfers among companies that are in various stages of engagement on finding and keeping female management talent, and this provides our members with a rich tapestry of experiences within the healthcare ecosystem.

Another initiative I am personally excited about is the re-launch of our Women in Science group in Basel. This is a peer exchange effort to help our women scientists make the transition to executive management, as well as to find ways to keep young female scientists engaged on the career path to top R&D positions, especially during the peak child-bearing years.

Pharm Exec: Does HBA take a position on policy issues in Europe, such as the campaign to mandate more female representation on private-sector corporate boards?

Graeve: We observe legislative developments but we are not lobbyists with the aim to direct laws or regulation. A key concern here in Europe is representation on boards, a movement that began in Norway a decade ago, when a diversity quota was introduced. The facts show that, despite the intent, the number of female CEOs in Norway has risen in the past decade from about 3% of publicly traded companies to 6%—not a big change. This suggests that legislation alone may not be sufficient to produce tangible results. The public debate induced by these efforts has certainly been valuable, but in the end what matters is whether the enhanced participation will actually lead to a working culture of female empowerment.

— William Looney

Front & Center

The New Hub: Managing Optimum Patient Services For Brand Success With Specialty Pharmaceuticals

Hubs provide an array of services and solutions to multiple stakeholders throughout a patient's treatment. What should manufacturers look for when hiring a hub?

The era of marketing blockbuster drugs to vast patient populations is largely over. Rather than hordes of sales representatives descending on physicians' offices, today's brand teams are increasingly tasked with marketing costly specialty pharmaceuticals to small disease populations. By 2018, seven of the top-selling drugs in the United States are expected to be specialty pharmaceuticals, compared with three in ten today.

The rapid growth of large molecule specialty drugs entering the marketplace for the treatment of complex, rare diseases calls for an entirely new marketing approach—more holistic, integrated and sustained. It also calls for marketers to service an entirely new stakeholder—the patient.

Close to 20 million Americans now have high-deductible health insurance that makes them responsible for the first $2-$5 thousand of spending. Consumers buying the popular silver and bronze plans on the federal exchanges bear 30 percent to 40 percent of the cost of their healthcare. The result? Patients increasingly view themselves as consumers (not patients) in charge of their healthcare choices, according to a recent report on Forbes.com.

As with any consumer product, much of the value for a specialty drug rests with brand recognition, especially when the manufacturer no longer enjoys patent protection, and other competing

Troy Koch, Executive Account Director

pharmaceuticals have entered the marketplace. Brand recognition for a specialty pharmaceutical (as well as for many small molecule drugs) is accrued by way of a positive and consistent patient experience. Better patient support provides a manufacturer with brand differential, better outcomes, and lowered healthcare costs. And for patients who may be suffering from a debilitating chronic illness, the support can be a saving grace, improving their quality of life, and perhaps facilitating a cure.

So, how does a manufacturer ensure optimum patient services to enhance the value of its brand?

Enter hubs, an effective mechanism for securing market share as well as a strategic approach to providing integrated services to patients, connecting them with physicians and payers throughout their treatment process.

Hired and funded by the manufacturer, patient-service hubs (also called reimbursement hubs) help patients navigate the process of obtaining permission to use, and reimbursement for expensive specialty therapies. Hubs have evolved and expanded their offerings over the last ten years to support patients from the moment of diagnosis and prescription, through access and reimbursement, to product delivery; then in assisting patients to stay on therapy via adherence programs, site-of-care transitions, refill requests, and data reporting.

What to look for in a hub

Hubs are dynamic, custom-designed entities. One size does not fit all. "What they are not is turnkey," said Troy Koch, Executive Account Director at Triplefin, a patient support services company. "Hubs are about evaluating and developing a program from a toolkit of services that can be mixed and matched to meet the distinct needs of a client. Speaking as a hub vendor, I try to step into the shoes of brand managers to understand the overall plan from their perspective. What are the performance indicators and their objectives of the brand? And most importantly, what does success look like to them?"

Koch made his comments at CBI's 4th Annual Hub Models and Program Design conference in February where he moderated the panel: "Assess the Impact of Reimbursement and Benefit Design on Hub Services."

Koch kicked off the panel discussion by asking his two panelists—both executive directors for market access at major biopharmaceutical companies—what a manufacturer should look for in a hub.

The panelists agreed that fit and flexibility were at their top-of-the-list requirements. "You have to be able to work very closely with a hub. So choose one that feels like an extension of you, which as an outsourced vendor they are," said one of the panelists. "Fit means being in sync with a manufacturer's culture—having a shared sensibility. Flexibility means being able to meet your needs as well as the needs of the patients, the physicians and the multiple other stakeholders, no matter what comes up during the marketing of your drug."

The panelists urged hub providers to forge a partnership with a manufacturer prior to launch and as early as possible in a drug's development.

"It's also incumbent on the manufacturer to know how the payers are going to actually reimburse for the product," added one of the panelists. "Many specialty products today are not on formulary. So, it would require a prior authorization and possibly an appeal, maybe two or three appeals.

"It's important then that you partner with a hub that has benefits optimization experience and can do great benefits investigations. Often times you can move that product from the BI that you got out of the hub over to your specialty pharmacy. You may still get a denial. You could have a denial for a number of capsules, price override, and a preferred pharmacy that's not in the network," said the panelist. "There are lots of things that could happen once it actually gets adjudicated. So even though you have the BI completed, you've got to have the hub and your specialty pharmacy communicating so that if they have to go back and do something in addition, say it's a capsule override, you can address that."

Following the panel, *Pharmaceutical Executive* asked Koch what "being a good fit and flexible" means from a hub provider's perspective?

"At Triplefin we provide patient access services that allow us to facilitate the manufacturer in getting that product to the patient, keeping them adherent, collecting information and providing support materials," said Koch.

"In some cases, with the addition of CompleteCare Pharmacy, which is owned by Triplefin, we add not only an initial enrollment benefit investigation with prior authorization, potential co-pay card or voucher, or free trial offer to initiate the product, but we also can deliver it right to the patient's door."

Triplefin is aggressively transitioning to being a first-in-class, full-service specialty services provider. The company has upgraded and expanded patient access, reimbursement and assistance services to include Rx365™, a suite of digital solutions that provides a single, unified platform for benefit verification, prior authorization, card activation and home delivery option. The company has also added a toolbox stuffed with web-based solutions that offer ease-of-use, better accuracy and comprehensive direction for every stage of the patient journey. In 2013, Triplefin became a subsidiary of H. D. Smith and part of their specialty unit along with Smith Medical Partners, a specialty distributor.

"As a hub, we have the breadth and the flexibility to be able to support and match all areas of a manufacturer's marketing objectives," said Koch. "For starters, manufacturers want a successful launch and to maximize entry into the marketplace. Manufacturers are trying to differentiate their product and educate providers about the benefits. At Triplefin, we created a dedicated call center for patients, a crucial component for our patient services operation, but we also designed a cost effective and efficient outbound calling program that focuses directly on physicians and functions as an adjunct field force doing tele-detailing, providing direct sample opportunities and territory warming through our call center. We also offer distribution services.

"We have one client where we are leveraging an integrated detailing and home delivery opportunity. We're approaching, through a pilot, the company's lower quartile providers. They have a traditional product in a crowded marketplace and they are not the market leader. And so by way of a free trial, they offer the product to patients through physicians who, in turn, gain experience on the product. If it is a positive clinical outcome for the patients, if it's tolerable, and the patients like it, brand awareness is built within a physician population where it might not have existed before."

Koch sees patient service hubs playing a more central role in maximizing outcomes, mitigating risk, and in providing an access venue so that patients are able to acquire affordable medications appropriately.

Photos: John Halpern

What's Real in Rare Disease

The rare disease space is often perceived as an easy mark for pharma, but our panel of Roundtable experts highlights the challenges of serving expectant patients in a more complex market access environment—staying power counts, so it's commit or quit

William Looney, Pharm Exec: *Rare diseases are life-threatening conditions affecting fewer than 200,000 patients. This may seem definably small, but in the aggregate, rare diseases are hardly rare: some 350 million people worldwide have a rare disease, more than the total for cancer and AIDS combined. We also know that 7,000 diseases are classified as "rare," yet only around 400 are currently treatable with medicines available in the clinical setting. In light of this daunting hierarchy of need, what stake has your organization taken in rare disease research and therapy, and why?*

Philip Ruff, Shire Pharmaceuticals: Shire has undergone a significant strategic realignment in the last year or so, but our commitment to rare diseases remains at the very heart of the company. Conditions like Hunter Syndrome, Gaucher's, and Fabry Disease are priorities, and our pipeline portfolio promises many additional growth opportunities in this space. All of us at Shire are aware of the intensely personal nature of rare diseases—as parents, we can relate to the fact that rare diseases affect children disproportionately. Shire also has a strategic focus on conditions where we know our scientists can make a difference. At present, we have 28 pipeline assets for rare disease in development.

Shire is shifting its organizational approach to rare diseases, from concentrating our work on rare diseases in a single business unit to one where rare disease products will be integrated with other products along therapeutic lines. For example, *Gattex*, the inflammatory bowel drug obtained through our recent acquisition of NPS Pharmaceuticals, will now sit in our GI business unit.

Mark Rothera, PTC Therapeutics: PTC is a biotech with a nearly two-decade commitment to the discovery and development of treatments for patients with rare disorders, utilizing our expertise in RNA biology and post-transcriptional control mechanisms. Our lead compound, *Translarna*, has been approved in the EU to treat patients with Duchenne muscular dystrophy (DMD) due to a nonsense mutation and we are in Phase III trials for its use in cystic fibrosis patients with the same mutation. It is estimated that 10-15% of an estimated 2,000 monogenetic rare diseases are caused by a nonsense mutation. We are assessing additional indications for *Translarna* for patients with the same underlying mutation. From an organization standpoint, in the last two years,

Roundtable Participants

Indranil Bagchi, Vice President and Head, Payer Insights and Access, Global Health and Value, Pfizer Inc.

Monica Martin de Bustamante, Managing Director, CB Partners

Doug Danison, Global Pricing and Market Access Head, Oncology & CNS, Takeda Pharmaceuticals

Sandeep Duttagupta, Principal and Vice President, CB Partners

Ted Haack, Managing Partner, Haack & Associates

Cindy McDonald-Everett, Executive Director and Oncology Global Therapeutic Head, Amgen

Mark Rothera, Chief Commercial Officer, PTC Therapeutics

Philip Ruff, Global Value Strategy Lead, Shire

William Looney, Editor-in-Chief, *Pharm Exec*

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Pharmaceutical Executive

PTC has moved from being privately held to a publicly traded company, providing the capital base to pursue our R&D goals as well as establish an international commercial presence. Our experience demonstrates that in the rare disease field, it's gratifying to advance patient-focused innovation for such high unmet need.

Indranil Bagchi, Pfizer: Pfizer has a robust presence in rare diseases, with 22 approved molecules that treat such conditions or carry status as an "orphan" drug. For example, we have a major presence in hemophilia as well as products for polyneuropathic conditions and Gaucher's disease. At Pfizer, our strategic focus in the areas of hematology, neuromuscular, and pulmonary has allowed us to find opportunities internally and externally to develop these franchises.

Doug Danison, Takeda Pharmaceuticals: I lead the regional pricing and market access team for Takeda Oncology. At Takeda, we aspire to make a difference in lives of cancer patients worldwide. My team is responsible for ex-US and ex-Japan regions, including EUCAN and emerging markets. As for rare disease, my team focuses on "rare" cancer. We are in the process of launching *ADCETRIS*, a CD30-targeted antibody drug conjugate in relapsed refractory Hodgkin lymphoma and relapsed refractory systemic anaplastic large cell lymphoma.

We try to focus our internal operations to deliver greater clarity, agility, flexibility, and focus around oncology, recognizing the different data requirements for many products in this segment as well as the growing importance of speed-to-market performance—which rests on our being able to anticipate the needs of market access decision makers at an early stage of development.

Cindy McDonald-Everett, Amgen: Throughout our 35 years as a company, we have focused on areas of high unmet medical need, including orphan therapies and indications through an integrated approach to commercialization that maximizes the potential market opportunities as well as benefits to patients. For example, we have a product with official orphan-drug status for chronic immune thrombocytopenia, a serious blood disorder. In oncology, we recently launched a product for a type of acute lymphoblastic leukemia (ALL), which by standard definition would qualify as an ultra-orphan therapy.

Overall, our approach in oncology combines both therapeutics and supportive care. There is a lot we can learn from companies that have built an exclusive franchise around rare diseases, but we also see that companies like Amgen, with a more diverse product portfolio, can leverage opportunities from this broader commercial presence, through the full product life cycle.

Ted Haack, Haack & Associates: I currently work as a consultant to the industry on various pricing, reimbursement, and access issues around the world. Most recently, I headed the Market Access function for Genzyme's rare disease business unit. Prior to joining Genzyme, I was Pfizer's head of pricing & reimbursement, primary care business unit, and acted as interim head of market access for PCBU from November 2011 through July 2012.

Looney: ***The common thread is that many diseases are now moving toward the "rare" category due to the impact of personalized medicine and the enhanced targeting options available through companion diagnostics. How does the work that CB Partners is conducting on rare diseases conform to these company assessments of the "state of the art" on rare diseases?***

Monica Martin de Bustamante, CB Partners: The definition of rare disease has evolved. It is more fluid today—even in chronic conditions one can find a rare disease indication, especially as pharma and biotech companies work to differentiate their target populations for a particular therapy with clinicians and payers.

The central question is why rare diseases have attracted strong interest from the industry. One factor is the high level of unmet medical need, which drives the focus on innovation. There is the reward derived from treating people who have few options, with special emphasis on the plight of vulnerable children whose lives can be cut short literally before they begin. Approval requirements and pricing and access challenges are markedly different, dependent on geography and the motivations of the various disease stakeholders interacting with industry. The small patient numbers place a premium on recruiting the right people for clinical trials as well as finding professionals with the knowledge to lead this work; both tasks get harder the larger the geographic remit in readying a global launch plan.

Standout factors

Patient advocacy is a distinguishing characteristic of the rare disease space. Patients are a force of nature in rare diseases. Because many rare diseases are complex and the community of victims is often obscure, it falls on active patients to set the terms of engagement on everything from trial recruitment to access and reimbursement. Productive partnering with patient groups is central to market success.

Much of the global agenda around rare disease was established with passage of the US Orphan Drug Act in 1983. The law sparked a surge in interest in these therapies, with more than 300 orphan drugs approved by the FDA after 1983 to date compared to only 34 during the decade prior to passage of the Act. Many countries have followed suit with their own rare disease legislation, including the EU, Japan, and, most recently, the emerging market countries—precisely where the industry is pinning most of its hopes for future growth. These are countries where payment conditions for medicines are difficult across the board, and especially so for rare diseases due to their association with nose bleed prices in the US and other affluent countries. Yet the long-term opportunities there are quite promising, if you do the required homework; each country is different.

Another critical element is finding that sweet spot with payers. Here the landscape is shifting, from a situation where payers remained willing to accept a high price point due to the small size of the covered population. Pricing aside, rare disease drugs were considered to be products of "low budget impact." Today, payers are rewriting the contract with the patient, shifting costs to individuals through higher co-insurance, bigger deductibles, and tiered co-pays, with the highest contribution pegged to the most costly brands. Other tactics include heavy use of prior authorization to slow access as well as outright exclusions from drug formularies—we estimate that about 15% of rare disease therapies are currently not available to US patients enrolled in the Medicare Part D drug benefit program.

In addition, the popular notion of "value" in drug therapy raises significant challenges in building the evidence base for a rare disease. It's frequently impossible to include an active comparator in your trial. Instead, you have to rely on a single-arm trial, probably at Phase II, due to the pressure that exists from patients to get the product to market quickly, because there is nothing else available. Yet that only makes dealing with payer expectations for metrics to demonstrate such "value" even harder. How can you prove a rare disease therapy is actually cost-effective when there is no accepted ICER (incremental cost-effectiveness ratio) to set a control group baseline against current treatments, where none such treatment exists?

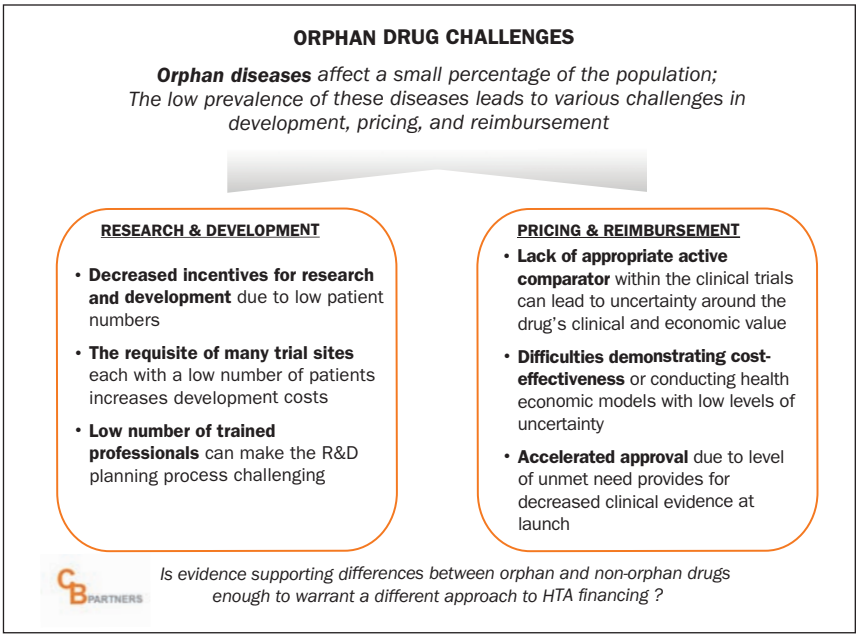
Three paths to access

Overall, the access environment seems to be coalescing toward three destinations. The first is through establishing an incremental clinical benefit, which is what France and Germany are seeking to do, where products obtain access when patients experience a clinical gain against what is currently in the market. The value/unmet need consideration must precede a discussion on price. Next, you have the budget impact environment, which has traditionally been a positive path to access in rare disease because price times small volume sales limits exposure to payers. The challenge here is that more rare disease products are reaching the market just as payers are placing caps on drug spend. If you keep adding new products, while the overall budget fails to keep pace, cutbacks in access are inevitable. While it is commonly assumed that a rare disease drug justifies a high —even six-figure—price tag, is this a sustainable model going forward?

The last—and toughest—environment is among those with a formal cost-effectiveness hurdle. The health technology assessment community is more comfortable with policies that earmark resources around broad chronic conditions like diabetes and CVD, when in rare diseases what works best is taking into account the level of unmet medical need. If a payer allows a discussion to focus on demonstrating clinical value, that's where you will see the best chance for access to a rare disease medicine. I see the cost-effectiveness argument being applied less rigidly, at least for ultra-orphan drugs that really have no alternatives. If such drugs offer a better quality of life, expressed over a five to 10-year span, that has to mean something to a payer.

All of this leads to a key strategic question, which is whether the distinctive characteristics of rare diseases require they be addressed through a separate regulatory channel or, alternatively, be evaluated much the same way as drugs for other conditions. Based on what I just said, do we need a tighter definition of what is "ultra-orphan?" It is worth noting that while most countries have opted to recognize rare diseases as deserving of special consideration and support, this does not guarantee an accommodating stance on P&R and access. Likewise, is it a good idea to press emerging country governments to prioritize a commitment to rare disease? If we put ourselves in the shoes of governments, with high public health expectations and limited resources, does that make sense? In some markets we might say yes, while in others it might prove to be a non-starter.

Finally, is it time for biopharma companies to refine their institutional approach to this part of their business? Do rare diseases require specialized expertise centered in a dedicated business unit or is it preferable to address the category through a therapeutic model?



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Front & Center

Adherence-Informed Clinical Trials to Optimize Drug Development

Electronic measurement and analysis of medication adherence addresses the greatest source of variability in drug response

The drug approval process is based on a key assumption: patients in clinical trials are reliably adherent to the dosing regimen specified in the protocol, and are thus optimally exposed to the test drug(s).

The reality has proven to be strikingly different. "Patient adherence in drug trials, like patient adherence in real world settings, varies tremendously," said Bernard Vrijens, PhD, Chief Science Officer, MWV Healthcare. "But if you don't measure and reliably evaluate adherence, you don't recognize deviations in drug exposure, and you cannot adequately and accurately explain trial results. We can no longer afford to ignore adherence."

When adherence is not monitored or is unreliably measured, it is generally assumed that adherence is nearly ideal in clinical trials. This view, however, is contradicted by extensive evidence provided by reliable electronic methods of measurement. Results from these methods, reported in nearly 700 peer-reviewed publications and cited over 47,000 times, show that suboptimal adherence is prevalent in ambulatory trials, in which outpatients are responsible for taking the drug according to the protocol-specified dosing regimen.

Pill counts are one of the earliest and longest-used methods to assess patient adherence. Despite the fact that returned tablet counts have repeatedly been proven to overestimate adherence because of prevalent discarding of untaken tablets, pill counts continue to be used as an adherence measurement, in addition to regulatory use for drug accountability in trials. Patient self-report

Bernard Vrijens

is affected by recall and desirability bias and is the second most frequent measure of adherence in trials.

The persistent use of inadequate or nonexistent adherence measurements in trials has created the following problems: failed treatment; inappropriate dose escalation; overestimated dosing requirements; emergence of drug-resistant microorganisms during anti-infective drug trials; hazardous rebound or first-dose effects; misdiagnosis when drug response is a diagnostic criterion; underestimated efficacy of the test agent; type 2 errors in judging efficacy; underestimated incidence of dose-dependent adverse effects; and distorted pharmacoeconomic analyses.

Trial sponsors who replace assumptions about adherence with reliably measured adherence data achieve more robust, more reliable and more actionable results. The effectiveness of pre-exposure prophylaxis for the prevention of HIV infection, for example, is highly dependent on adherence. Trial data for the leading pre-exposure prophylactic agent showed less than 50 percent efficacy until adherence data was evaluated. A subgroup analysis showed 100 percent efficacy and more than 95 percent adherence when using MWV's Medication Event Monitoring System (MEMS™), which monitors, measures and analyzes patient adherence for real-time adherence-based adjustments during the trial. In this example, reliable data analysis was instrumental in transforming trial failure into successful product approval.

The MEMS system utilizes "smart" packaging that electronically tracks medication-taking behavior and wirelessly transfers the data to a state-of-the-art, statistical analysis system. The MEMSCap can be fitted to any standard drug container. Today, smart packaging is available for monitoring adherence with different form factors, including blister packaging, injectable medications, and inhalers.

MEMS was created to measure and manage adherence in clinical trials. The primary objective of using MEMS in drug development is to get the best possible estimate of efficacy and safety, and finally the best possible pricing, strictly based on objective measures. The effectiveness of certain hepatitis C medications, oncology treatments, anticoagulants and other narrow therapeutic index agents is intimately related to adherence. Monitoring adherence, including the time of dosing, provides clinicians and sponsors with a true, evidence-based picture of dose-dependent drug response, adds efficacy data, helps to identify the appropriate dose, and underlines the need for adherence to achieve

> Patient adherence in drug trials, like patient adherence in real world settings, varies tremendously," said Bernard Vrijens. "But if you don't measure and reliably evaluate adherence, you don't recognize deviations in drug exposure and you cannot adequately and accurately explain trial results. We can no longer afford to ignore adherence.

effective treatment in clinical use. Adherence-informed trials using MEMS are an effective vehicle for moving through the drug approval process.

The pharmaceutical industry recognizes that adherence generally declines over time in clinical practice. Similar declines in adherence in clinical trials have largely been ignored. Under-dosing, the most common form of non-adherence, simultaneously decreases the effect size and increases the variation in effect, which in turn weakens statistical power to the extent that proof of efficacy cannot be established. The drug candidate often fails because of lack of efficacy resulting from patient non-adherence to the test drugs.

Some study protocols attempt to compensate for non-adherence by increasing the specified dosage(s). Higher dosing may induce unacceptable toxicities in adherent patients, leading to a safety profile that overstates the potential for adverse events. Elevated adverse event rates are a leading reason promising drug candidates fail the trial process.

Adherence data becomes increasingly important as drug development focuses on targeted therapies with narrow therapeutic indices, in which the drug response is both dose and time dependent. Depending on the half-life of an agent and the therapeutic index, the timing of a dose can be as important as whether or not the dose was taken.

Adherence is a three-part process—initiation of treatment, implementation of the dosing regime, and eventually discontinuation.

In clinical practice, *initiation* is the key barrier. On average, 20 percent of patients never pick up their initial prescription. Patients in clinical trials, however, are highly selected and have given informed consent. Trial participants sometimes have higher motivation to *initiate* treatment than in routine care.

But once the trial begins, participants tend to revert to daily routines, and *implementation* is impacted. They forget doses. They get too busy to take a dose. They are uncomfortable with side effects, real or perceived, and take a drug holiday or stop treatment entirely. And like patients in clinical practice, patients in trials typically fail to mention their lapses to trial staff.

Unfortunately, trial analyses are based usually on the intention to treat, a methodology that assumes perfect adherence to protocol. Dose-ranging studies, safety and adverse event profiles, equivalence studies, comparisons with active controls and most other outcome results are based on an underlying assumption of perfect adherence. Poor adherence skews trial results toward failure.

Regulators recognize the problems that non-adherence brings to trials. In 2012, the U.S. Food and Drug Administration (FDA) issued draft guidance on "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products." FDA called on trial sponsors to decrease heterogeneity by first identifying and selecting patients who are likely to adhere to the dosing regimen as specified in the protocol and second, by boosting adherence through the use of smart packaging that monitors drug use during the trial so patients can be encouraged to be more adherent.

Adherence is a behavior that can be learned, encouraged and reinforced by habits. Prompt feedback and education can increase adherence by 20 percent or more in individual patients.

This enhanced adherence can help optimize drug response and reduce residual variation to increase the statistical power of the trial. Adding adherence monitoring to a trial protocol can do more to increase the statistical power of a study than simply increasing patient numbers with the same unknown variability in adherence.

"You cannot predict adherence, but you can measure it," Vrijens said. "When you measure adherence, you can manage it to reduce its negative impact on efficacy and safety. Adherence-informed drug trials give you more robust, more reliable and more actionable data."

Reference topic: http://goo.gl/6Z4qlH

For more information on this research, please reference: Vrijens B, Urquhart J. Methods for Measuring, Enhancing, and Accounting for Medication Adherence in Clinical Trials. *Clinical Pharmacology and Therapeutics.* 2014. 95(6): 617–626

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I am not sure the group can resolve these questions today but they, nonetheless, carry important implications for future success in this space.

Time for new models

Looney: ***Any comments on this overview of the issues? Will payers keep on paying?***

Bagchi: We might be too complacent about budget impact. Even if we present decent cost-effectivencess data, if you cannot convince the authorities the budget will not bleed, you will not get access to reimbursement. More flexible analysis of cost-effectiveness should be adopted that balances other considerations such as equity, the rule of rescue, community values, patient needs, and the long-term costs avoided as a result of access to treatment. The process for assessing new therapies for rare diseases should be efficient, fit-for-purpose, transparent, and informed by community and patient values.

Ruff: There is a basic disconnect between the pace of medicine innovation and the way our health systems register the cost of innovation. Technology is advancing to the point where, for example with the emergence of gene therapy, we are potentially close to being able to provide a cure for some rare diseases that originate in genetic abnormalities. The cost for such a cure in a rare disease would tend to be very highly priced. US payers then have to face investing a significant sum in a patient who may not remain within their plan long enough for them to accrue the full long-term financial benefits of such therapies. Patients in a US healthcare plan typically remain with that plan only for two to three years on average. Such new technologies are likely to have a profound effect on our healthcare system.

Haack: The average annual profit margin in US managed care is about 1.5%, after tax. A big ticket, big population drug like *Sovaldi* suddenly enters the picture, so what happens to United Healthcare, with its $110 billion of revenues? It just lost a full percentage point off its profits.

Bustamante: This is a reality for all approaches to financing healthcare. The UK NHS touts its lifetime cost of care health model, but the financial commitment is always contingent on the annual budget cycle. There is no systematic attempt to balance current liabilities against lifetime savings.

"If such drugs offer a better quality of life, expressed over a five to 10-year span, that has to mean something to a payer."

—Monica Martin de Bustamante, CB Partners

Bagchi: The industry must work harder to develop new payment models. An amortized risk exposure model is one interesting approach. It certainly has application to gene therapy, whose effects are truly long-term—if you can't amortize the cost, there is no sustainable way for society to pay. This is clearly on the radar screen, as a new gene therapy costing in excess of a million dollars per course of treatment is becoming a reality.

Opportunity knocks where?

Looney: ***Rare diseases do not conform to geography. Given the structural financing issues we have just highlighted, which country markets represent the most compelling market opportunities? Is it still the US and the European Big Five?***

Rothera: Japan has to be included. It recognizes orphan indications and is willing to reward innovation for small patient populations. I also see potential in key emerging country markets, especially Brazil.

Bustamante: To the extent R&D investment drives the rare disease space, pharma companies must rely on markets where pricing is sufficient to finance it. That includes, in addition to the US, the EU five, Japan, Canada, Australia, Brazil and Turkey. Despite the buzz, it remains difficult to build a core rare disease business around emerging countries.

Ruff: It really depends on the profile of each rare disease; in some countries, the incidence of a rare disease is disproportionately high due to the confluence of many factors, from epidemiology to the environment shaping the gene pool. The attention these diseases get from governments also matters.

Haack: The epidemiology profile is important. When I was at Genzyme, we looked carefully at the numbers for one of our key rare drug therapies, indicated for treatment of Gaucher's disease. The global population with this condition is estimated to be around 35,000, of which a good number are located in China, a market that presents significant challenges to diagnosis. We estimated that only 8,000 patients worldwide were being treated, despite decades of enzyme replacement therapy (ERT) availability. So where was everybody? The discrepancy led us to conclude the size of the affected population is probably overinflated. We had the opposite situation with Fabry's, another inherited genetic disease that is usually fatal at an early age. After diagnostic screening began for Fabry, we learned very quickly that the epidemiology data was lower in many places than what the diagnosis rate showed. The screening of newborns showed that this rare condition was actually quite prevalent in some countries. Maximizing market potential depends on getting the

epidemiology right, at the start so that budget impact can be better determined.

Ruff: The challenge in rare diseases is that our understanding of epidemiology is constantly evolving, which complicates our ability to meet payer expectations about budget impact.

Haack: It also affects the calculation of the payer: are we on the right side of the lump sum versus annuity equation? If a drugmaker treats a child with a rare disease at 18 months and that child goes on to live a normal life, that's an awesome annuity—for the child and for the drug company. But the good deal may not be seen as such by the payer, who has to bear the full cost of treatment over that lifetime.

Rothera: I'd also like to point to the increasing reliance on clinical trial enrollment criteria in determining the label for treatments. Even in rare diseases for very small populations, epidemiologic data allows us to identify sub-populations with a distinct clinical phenotype that can lead to a restriction of access to therapy when a larger population may benefit but were unable to be included in the clinical trial. An example is treatment for certain patients with ERT. Because ERT's are unable to cross the blood brain barrier, they do not address the CNS component of the disease. If CNS symptoms develop significantly, it can force the discontinuation of treatment. Again, how do you build that into the predictable budget impact scenario demanded by payers?

McDonald-Everett: Finding balance around pricing for diverse indications on the same product is another issue. Payers tend to apply a blunt tool when it comes to pricing. Establishing value in each indication and negotiating the right price point for a later indication can adversely impact pricing for the broader population—how do we ensure there is equitable access, at the right price, for both groups? It requires a lot of internal debate about the exposure risk if you don't get this right with payers. There are various mechanisms that could be considered: forgo seeking a high price tag for the smaller rare disease population, or promote access through patient assistance programs and donations, to minimize the effect that a high ex-factory price might have on price negotiations for the much larger indication? There is no easy way to address this.

Bagchi: Looking at the geographic spread, it's hard to make generalizations about rare diseases. I agree that the main market potential remains in the mature industrial markets, but there are some interesting twists. In sales of our hemophilia business, the US and the UK are at the top, but right up there with them is Iraq. And the Iraqis pay on a national tender basis; it's all government money and of course that also means some subsidization through independent donors and foreign aid.

"Our understanding of epidemiology is constantly evolving, which complicates our ability to meet payer expectations about budget impact."

—Philip Ruff, Shire

Kickstart financing

Looney: ***This implies a much wider range of stakeholder groups are involved in facilitating access to drugs for rare diseases—similar to vaccines?***

Bagchi: Yes. Our outreach has to involve NGOs, foundations, international organizations, and governments. As innovators, we have to be creative in finding these non-traditional sources of funding.

Haack: Actually, creative funding is as critical as producing the studies to demonstrate clinical relevance and cost-effectiveness. You have to establish where the local funding stream is going to come from, right at the start of your commercialization strategy; certainly well before registration.

Looney: ***We have spoken a lot about price and access, but what about issues that relate to development, particularly cycle time to registration? Aren't you living in a charmed world? Certainly there is a perception that regulators like the FDA are very supportive of rare disease medicines.***

Bustamante: The FDA is usually quite flexible in the design and end point designations on clinical trials for rare diseases. It knows that reality requires some departure from the typical standard large population trial for CVD or diabetes. The key challenge is how this activity relates to the next step, which is obtaining patient access for an approved product.

Trials and tribulation

Ruff: It is widely assumed that, because rare disease trials usually involve a small group of subjects, it is cheaper to run them. That's not really true. Most trials that Shire conducts on rare disease have to be managed at numerous locations, across geographies. Finding qualified investigators is hard, especially outside the US, where major hospitals and other centers of expertise are often scarce. Here in the US, a patient we recruit might live 60 miles from a study center. In Latin America, that person can be two days journey or more away from the site. And as our trials often require children, there is extra overhead in including parents and other care-givers in the mix. Sometimes we have to move entire families to a trial site be able to get a patient to take part in a trial. This can be a complicated and costly process.

Rothera: Determining the proper endpoint for a rare disease trial is a pro-

cess in itself—what are you actually testing? You cannot depend on the FDA to make that call for you. It has to be built by you, with the help of top experts in the field, with a design that can be validated through to final regulatory approval. We had to pioneer the development of a validated clinical endpoint for DMD—the six-minute unassisted upright walk—working with the DMD community. The endpoint has since become the standard for other DMD clinical trials.

Bagchi: Most rare disease patients lack treatment alternatives; usually, their condition is life threatening, and many of these patients are children, too.

"Determining the proper endpoint for a rare disease trial is a process in itself—what are you actually testing? You cannot depend on the FDA to make that call for you."

—Mark Rothera, PTC Therapeutics

The result is strong resistance to being in a controlled blinded study where there is an even chance of the patient getting the placebo. What does this mean for the sponsoring company? Your trial is essentially competing with compassionate use programs. That's the goal for a desperate parent—you don't want your sick child to be in the placebo cohort. From an approval perspective, it carries a real implication. The access you give to a half dozen children can skew the findings and delay getting the test drug to market, where ultimately many thousands of children will benefit.

Looney: ***Is there an easy fix from regulators to allay such an outcome?***

Rothera: The early access model applied in some European countries—like France or Italy—is an approach I'd like to see adopted in the US. Your ROI begins a little earlier, patients get quicker access, and it facilitates finding a sustainable price level, while not compromising the implementation of fully validated trials required for regulatory approval.

Bagchi: The other approach being tested in the EU is adaptive licensing, which is now the subject of a pilot program—involving several rare disease compounds—administered through the European Medicines Agency (EMA). The essence is to merge the interests of regulators and payers by granting contingent marketing rights to a drug developer in return for a commitment to additional testing—in short, coverage with evidence development (CED). So the company gets access, it conducts studies according to protocols approved by payers, and the payer can apply the results to negotiate a final market price or change the terms of access. I would say discussions are still tentative, largely because national reimbursement authorities are hesitant to devolve their responsibilities on price and reimbursement.

Haack: It's hard to see any real incentive for industry to play the adaptive licensing card. Most government participants view it as a way to short producers on price. Certainly, prices are never going to rise in response to real-world evidence that proves a medicine delivers what it promised. There has been discussion by certain governments of allowing the price to come up to an appropriate level, but the "launch price" would be lower than that.

Does France do it better?

Looney: ***Is there any market where we agree the stars are aligned toward doing things right in supporting rare disease innovation that delivers for patients?*** (Editor's note: the entire group agreed that France presents "an interesting dynamic.")

Bustamante: The French ASMR rating system puts a metric value around societal unmet need in a way that other markets do not. It accepts the idea that if there is no treatment available for a rare disease, and your medicine offers a chance for clinical benefit to the patient, then value is demonstrated.

Rothera: France was one of the first countries to single out rare diseases with a comprehensive national action plan. That plan has been amended several times to keep pace with the science.

Bagchi: In France, there have also been some new developments. The most important is a new rule requiring that any medicine costing more than €50,000 a year per patient undergo an intensified budget impact review. This is a key consideration in developing an early access plan.

Looney: ***Is this trend likely to spread to the US? Will the Patient Centered Outcomes Research Institute (PCORI) end up serving as a cost-effectiveness watchdog on rare disease drugs?***

Ruff: I sit on PCORI's rare disease panel. PCORI is not authorized to consider any issue relating to pricing or cost of therapy, except when it relates to direct patient out-of-pocket costs. There would need to be a significant political shift in the US to introduce cost-effectiveness criteria as used by many other other countries.

Power points on pricing

Looney: ***Is the industry neglecting any useful arguments to justify the pricing of rare disease medicines and strengthen the value proposition behind them to patients and payers?***

Rothera: Medicines for rare diseases amount to only about 2-5% of overall drug costs in the US and Europe. The budget impact is manageable and it supports a lot of innovation in areas of high unmet medical need, whose benefits are incalculable over time.

McDonald-Everett: The improvement in quality and productivity from medicines innovation, including the life years gained, as well as the general societal benefits that derive from this, are components of value that are usually overlooked. The math is always built around the next budget cycle. This is the psychology that we have to change.

Danison: We need to consider how we communicate the price of our products. We have seen the *Sovaldi* example where there was pushback about "a thousand dollars per pill." However, when you consider the cost to treat HCV it may have been perceived differently. Communication and framing of the drug price may have helped them. In an ideal world, it would be great if we could move away from such a focus on price per pill, per vial, etc. We must think about what it takes to have better health outcomes for patients more than counting up vials and pills. However the existing infrastructure is focused on units, so a lot of work would be required to remove the limitations of existing billing and coding systems, especially in the US. But, at the end of the day, the focus should be on delivering results for patients.

Haack: There is another issue hiding in plain sight—soaring company valuations and the rich premiums being paid for licensed products. Pharmacy benefit managers (PBMs) and insurers think that if a drug company has just paid several billion dollars essentially to acquire one new product, that company is going to have make a lot of money very quickly. True or not, it's a perception.

Practice with patients

Looney: ***The patient can serve as an important intermediary to this discussion. Clearly, patient organizations are critically important in focusing attention—and research dollars—on rare diseases. What is the current state of the industry's relationship with patient advocates? Are we in the midst of any significant changes in the way the two of you interact?***

Duttagupta: A trend is the discomfort of some payers about overt efforts to mobilize patients as advocates for rare disease treatment. This is particularly evident outside the US. In Europe, for example, patients are still not perceived as a social partner in health, deserving of a seat at the negotiating table. Despite this, patients have in fact become far more global in orientation. In the hemophilia space, chapters of the Hemophilia Foundation have spread to virtually every major country. Local groups can be mobilized quickly on behalf of issues that impact patients.

Rothera: Our experience in DMD underscores the critical importance of patient advocacy. Organized patient involvement clearly helped push our technology over the registration line by highlighting the enormous unmet need and the natural history of this fast progressing disease. That in turn spurred support for the widest possible access to the drug. I would add that we were able to leverage the passion and awareness of the Duchenne patient community to accelerate recruitment to our clinical trials on the basis of the right genotype.

Bagchi: Rare diseases are an exception to the fact that in most of the large therapeutic areas, patients remain an afterthought. Patients have not been fully integrated to the FDA approval process, even though recent legislation mandates more consultation. There is a need to apply the positive lessons we have learned in rare diseases to the broader arena.

Rothera: The Parent Project Muscular Dystrophy, a family-centered network, recently funded a benefit-risk assessment survey—involving approximately 120 caregivers—that was designed to measure their tolerance for potential benefits and risks of emerging therapies for DMD. Most patients with this relentlessly progressive and terminal disease will die in their 20s or 30s. Preserving patients' muscles and abilities at any stage of the disease is valuable to the caregivers. The insights from the survey have gotten the attention of the FDA and may inform its decision making as it reviews potential therapies that slow or stabilize progression of the disease.

Danison: Patient insight is particularly critical as we move toward a financing system that relies more on individual contributions to the cost of care. These insights are particularly important, for example, in the US, when there are both oral and IV alternatives with different out-of-pocket responsibilities for the patient. Patients have preferences; we should understand them.

"Rare diseases are an exception to the fact that in most of the large therapeutic areas, patients remain an afterthought."

—Indranil Bagchi, Pfizer

Bagchi: Again, I see a disconnect between reality and intent. Patient reported outcomes (PRO) are seen as a valuable source of insight, but when such data is collected in a study trial, how much of it ends up on the drug's label? Do payers consider the data when mulling reimbursement? It's not clear that they do. Standardized PRO instruments exist, but acceptance into wide use requires endorsement by all parties, including regulators and payers, which is not the case. The burden usually falls on the investigator to develop the PRO and then ensure its dissemination—an expensive task.

Ruff: The absence of a uniform PRO standard is a problem. Much is left to interpretation: is it really a PRO? Or is it a caregiver-reported outcome? Or a physi-

cian-reported outcome? You also cannot expect a child to fill in a questionnaire, so the parent does it. Is that a parent-reported outcome? I think an FDA regulator would tell you that a response from a physician carries more value than that of a patient, especially if mom and dad are really doing the reporting. There are clear guidelines around PROs in general. The issue is which type of instrument will capture the most appropriate data that is meaningful to patients, physicians, regulators, and payers.

"Discussion on company size or portfolio diversity ignores what really counts, which is whether the organization is a learning organization."

—Cindy McDonald-Everett, Amgen

The optimal organization

Looney: ***We have not addressed the impact of size, scale, and internal organization in fostering a culture of excellence around rare diseases. Does the way a company manages its stake in rare disease therapy affect its capacity to be a successful competitor in this segment?***

Rothera: There are issues with size. In the 17 years I have worked in rare diseases, I have seen multiple instances where large players simply abandoned work on an orphan drug when the initial trial results proved less than expected. What you need most in rare diseases is determination and resilience to stay the course. That means in turn a higher tolerance for risk, which is often absent in big Pharma, where multiple options force you to make tradeoffs.

Haack: Culture does count. I worked for Genzyme. I can say that a condition for being hired there is the ability to prove how well you think about the patient in your daily work. I also worked for Pfizer, whose culture is very customer-focused; it's the clinician and provider that is top of mind. You need to be both patient and customer focused in genetics now. Genzyme eschewed bureaucracy, while Pfizer had more resources to bring to a situation.

Rothera: Rare disease is very global. Being flexible, with ears close to the ground, is vital to keeping connected to the geographies where you choose to engage. Staying small means having fewer silos that thwart these connections.

Bagchi: When initially organizing our rare disease portfolio, Pfizer evaluated a number of potential approaches. These ranged from continuing the arrangement in which rare disease drugs had no special designation to various models of alignment and operational independence. We opted for a course designed to best align both to the shape of our portfolio and to the innovative core of Pfizer, with its own R&D and commercialization staff assigned to push specific targets forward and create better synergies with rare disease patients. This arrangement gives us the proper balance between scale and flexibility, while the enhanced focus allows for stronger links back to the patients that inspire our work.

I have asked payers—and structure and size do drive perceptions of the business. For example, when payers are asked if the same rare disease compound, with equivalent support data, was put to them for a reimbursement decision simultaneously by a big Pharma company and a small biotech, which one would they choose; many have said they would opt to go with the biotech, on grounds that it was smaller and presumably had more at stake in succeeding with the compound than a big Pharma. The sentiment was to "give back" to the biotech, assuming it had put more effort and skin in the game; it is a calculus that causes bigger companies to confront more negative risks than is commonly assumed.

McDonald-Everett: Discussion on company size or portfolio diversity ignores what really counts, which is whether the organization is a learning organization. The advantage for a company with a more diverse portfolio is the opportunity to leverage best practices from a broader portfolio and apply it to rare diseases, and vice versa. The requirement is you have to reinforce communication across functions and geographies. No silos.

Rare disease—future tense

Looney: ***As a final thought, what excites you about the future of science in rare diseases? In what therapeutic areas is our industry best positioned to help fight these conditions?***

Ruff: Gene therapy holds significant promise, largely because it will serve as a pathway to cures, not just in our space but in other areas of medicine as well. I believe that we will see significant progress, in a 10-year time frame rather than over multiple decades.

Duttagupta: It is also going to drive enhancements in personalized medicine, which means these cures will lead to broader service and financing efficiencies because of the higher level of certainty attached to the treatment.

Danison: With an increased focus on personalized medicine, we will see treatments for cancer classified more according to the mutations that drive a tumors growth rather than the location where the tumor originated.

Rothera: mRNA biology will prove just as important as unlocking the secret of DNA many decades ago. PE

Editor's note: The views expressed by the Roundtable participants are their own and do not necessarily represent the official positions of their affiliated companies.

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Compliance at the Cross-Border Crossroads

Increasing demands for transparency have seen the role of chief compliance officer (CCO) evolve rapidly over the last 10 years. But the upcoming shift to cross-border compliance in Europe will present CCOs with their biggest challenge yet. By Julian Upton

Compliance, across all industries, thankfully no longer occupies its 1980s position as a "corporate backwater." Back then, a senior banker recalled for the *Financial Times* (FT, April 24, 2014), the compliance specialist at one London firm "was also charged with looking after the boss's wine cellar," such was the general vagueness and perceived irrelevance of his nominal role. In pharma around the same time, a chief compliance officer (CCO) was a rare commodity indeed. As Ilyssa Levins and Eve Costopoulos write on the *Pharmaceutical Compliance Monitor* website, before the late 1990s, US companies, for example, simply formulated their business practices on their understanding and interpretation of an anti-kickback statute that was exceptionally broad.

In banking, what the FT calls "the tsunami of regulatory initiatives" that followed the 2007–2009 global financial crisis saw compliance move out of the shadows and toward center stage. Transported through time to 2013, that 1980s banker would no doubt have been astounded to hear a major UK bank (HBSC) announce its plan to hire more than 3,000 compliance officers.

Pharma, of course, has also intensified its compliance activities in the last few years, even if this has been, as with banking, as much a reaction to external regulatory and legislative pressures as a desire to get its house in order.

Recently, we have seen the rollout of the Sunshine Act's Open Payments database and the European Federation of Pharmaceutical Industries and Associations' (EFPIA) call for its 33 national member organizations to disclose details of payments made to named individuals and publish them in open registries by 2016. Add to these

initiatives a growing emerging market crackdown on bribery and corruption, and it's fair to say that compliance is an industry hot topic. The Economist Intelligence Unit has predicted that more than 70% of pharmaceutical sales this year will be made in countries with transparency regulations. And aside from GlaxoSmithKline's widely reported woes in China, pharma companies are currently under investigation for corruption in countries as unlikely as Syria, Iraq, and Lebanon.

In January 2013, *Pharm Exec* wrote that compliance "is no longer just a box to check—its strategic function within the organization is more important than ever." By extension, we added, "chief compliance officers are gaining momentum and have moved from the background of business operations to the foreground."

So, two years on, can we confidently say things have moved on for the CCO?

Compliant with compliance?

For David Eves, director of medical affairs and compliance at Chugai Pharma UK, there is a much greater understanding across companies of the centrality of compliance to everyday business activities such as the separation between promotional and non-promotional activities. "Everyone knows the importance of the Code," he says. "No one has come to me recently and said 'Can I do this? I'm not sure if this is within the scope of the Code.' Everyone knows what they *can't* do. But there's a general view now that compliance should not be a business disabler—it should be about finding solutions. There's an increasing awareness that it's vital to be an ethical business that is top-down, bottom-up and about perception."

However, Garineh Dovletian, chief risk officer at The Medicines Company (Parsippany, NJ), a mid-size pharma focused on the acute/intensive care hospital market, believes the boundaries of what fall within compliance are less clearly delineated than they were 10 years ago. "I find it harder to define where compliance begins and ends," she says. "I can recount what the Office of Inspector General (OIG) guidance says, or what the US Sentencing Guidelines say, or what the Organization for Economic Cooperation and Development (OECD) says about what the role should be, but that's just the starting point." Whether it's working with finance and procurement team in terms of Foreign Corrupt Practices Act (FCPA) compliance and proper controls, or with clinical team and activities surrounding research and post-approval, Dovletian believes the role of the compliance officer is getting broader.

"Everyone knows what they can't do. But there's a general view now that compliance should not be a business disabler—it should be about finding solutions."

But is it taken more seriously? On this point, Siemens' CCO Dr. Klaus Moosmayer told C5's online blog (September 2014): "I am optimistic, but I'm not naïve … we are certainly not at the end of the way to achieving this." He said that the question of whether compliance is seen as bringing business value is still a developing topic. Even now, the major day-to-day challenge of a compliance officer is getting support from middle management. Dovletian agrees: "If you don't have buy-in from the organization's mid-level leaders, you're dead in the water from a compliance perspective," she says. Mid-level managers are close enough to their employees to set the tone of the day-to-day operations; getting their backing is an issue that, for some companies, still needs more attention.

CCOs still wrestle to get their execs on board. Speaking at CBI's Compliance Congress in Brussels, Belgium, last year, Abbott's L. Kathleen Durousseau said she had moved away from trying to get staff to read policy and procedures, favoring instead activity-based tools. "A decision tree helps people understand. It lets the commercial person, for example a senior-level marketer, do a lot of the work themselves," she explained. Mundipharm's UK Compliance Officer Kelly Hawson, speaking at the same event, stressed the need for everyone "to take ownership of compliance," to practice accountable leadership. Failing that, appealing to people's self-preservation instinct tends to work as a bottom-line approach. Sometimes, added Hawson, "There is a point where you just have to say, 'These are the company rules.'"

As the saying goes, there's nothing like the threat of jail time to make an executive "get religion."

These struggles are endemic, however, and, perhaps, to be expected; after all, most heads of department have to be inventive in getting their organization on message. For Polaris Management's Marc Eigner, a vendor who has long worked with pharma compliance departments, CCOs are now more ensconced in the c-suite than they were a few years ago. He points to the rise of Actavis head Brent Saunders, who began his career in pharma compliance. "To see someone with a compliance background become CEO sends a clear message," he says. Much of the CCO's increasing recognition has been down to importance of commercial compliance. "In the past, the commercial aspect of compliance was not as big a deal to the CCO as, say,

manufacturing compliance or government pricing," says Eigner. "But now we're finding that it has become the most significant part of the CCO role."

Data from the PwC report Compliance in 2025 reveals that 84% of pharma companies now have a CCO, reporting directly to the CEO. PwC's Sally Bernstein and Andrea Falcone picture the CCO as "the c-suite star of 2025;" by that time, they write, "the chief compliance officer will sit right at the very center of the seismic shifts reshaping business [and] will be a much closer confidant to the CEO, a permanent member of the leadership team, and a sought-out risk advisor when strategies are being set. Their voice will hold sway, and their wisdom will contribute to the resilience of the organization."

That all sounds promising, but 2025 is still 10 years away; in the meantime, many compliance departments do still have mountains to climb—even the biggest of big Pharma is a long way from matching HSBC's pledge for 3,000 compliance officers. Mid-sized Mundipharma, for example, has one full-time compliance officer and 11 part-time. But The Medicine Company's Dovletian resists the urge to differentiate the compliance officer role based on the size of the organization. "We're a company of approximately 700 people and we have the same kind of transactional complexity as you would in a large company," she says.

From a compliance-solution vendor perspective, Eigner agrees: "You might think it is harder for a small company with a smaller budget to get a compliance system in place, but the reality is they have far fewer roadblocks." Big companies may have larger budgets, but they also have "many more systems and many more people who have been used to doing things the same way for 30 years." Consequently, explains Eigner, getting things done in a big company can involve a lot of politics.

Eigner notes how, in smaller companies, customer master systems and finance systems are often "in their infancy," so getting the requirements embedded into these systems upfront can be easier. He points to venture capital-backed pre-approval companies "that are automating the entire end-to-end engagement process even before they have a product." If you're a specialty pharma company that wants to eventually be purchased, "the one thing that can thwart your chances is the threat of a $2 billion CIA or FCPA violation."

"The chief compliance officer will sit right at the very center of the seismic shifts reshaping business [and] will be a much closer confidant to the CEO."

For Dovletian, it is "a bit naïve to define the CCO job based on the size of the organization. Whether you have one transaction or 100, you still require competency to do it right." Indeed, a big company could still be confined to one therapeutic area in one market and have a simple structure. But a smaller firm like The Medicines Company, Dovletian explains, is active in many different countries, many different therapeutics areas, and in different phases of development. Consequently, like the biggest pharma companies, it needs a compliance strategy that can be effectively rolled out globally.

Is a global compliance strategy possible?

With regulation of the disclosure of healthcare professional (HCP) spend an increasingly cross-border activity, the question remains of whether a global compliance strategy is really achievable, particularly in high-risk markets such as Syria, Yemen, or Russia, for example.

"It's very hard to manage a customized approach to each country," says Dovletian. "So templates should be standardized, and a code of conduct should apply consistently. You need to give people some predictability; if you want adherence to process it can't be too disjointed." Dovletian advocates the "grandmother test" as a "go-to test that can be applied consistently" across borders. Basically, you ask yourself the question: "How would I feel about a certain activity if it was affecting my grandmother?" This "helps you think a little more carefully about the long-term impact of your activities," she says. But, she adds, if there's a will to circumvent, it will happen no matter how strict the rules are. "If your incentive structures reward behavior that encourages short cuts or is aggressive, you're putting people in a day-to-day dilemma."

The global-standard theory sounds sensible enough, but in practice there remain significant obstacles to streamlining compliance across borders. Europe alone presents enough challenges to keep compliance officers awake at night. Inconsistencies across the region in terms of definitions, templates, and, not least, languages and cultures, will make the integration of the new EFPIA code something of an ambitious task to say the least.

Central to how a European country responds to new disclosure requirements depends on its "historical baggage," says David Eves. "If you look to Scandinavia and the Netherlands, those countries appear to be more OK with transparency, but elsewhere this can create a major concern at a personal level." (The Netherlands' national body, Nefarma, had set up its central database and published its first register by April 2013,

more than three years ahead of the required EFPIA deadline). One senior UK compliance officer commented recently that Central and Eastern Europe (CEE) is the region that "makes me most nervous." She added: "Everyone has a moral compass, but trying to get a message across to staff in CEE that something is wrong when they in fact believe it is OK would take a very long time. You have a brick wall to break through if they think it doesn't affect them."

The biggest challenge in Europe is having databases of physicians that are reliable and regularly updated. Where, in the US, "you did not tend to see redundant multiple systems within one company," says Eigner, "in Europe it's the norm for a company in one country to have, say, three to five financial systems." He goes on: "I don't think I've seen a single large company yet that has less than four or five customer masters within Europe."

Even Western Europe's heterogeneity and multilingualism can work against it. "Someone from Switzerland could be engaging with a French HCP and not realize it," says Eigner. "The HCP might have a residence in Switzerland, and everyone is speaking French there, but he or she is a licensed French physician and subject to the demands of the Loi Bertrand (France's "Sunshine" Act). This is something we're going to start seeing in the next couple of years."

All this, adds Eigner, is new territory, even for major pharma companies. "This is the first time you're really seeing major companies moving to put a global transparency and global HCP engagement strategy in place," he says. "Even though there might be a global policy in place, the specifics have not been standardized." CCOs, then, have to ask themselves some questions: Are they solving a specific issue within compliance such as transparency? Or, for example, are they trying get HCO/HCP engagement standardized across the globe? The biggest challenge before formulating a global strategy, says Eigner, is addressing fundamental questions like these.

Technology is all well and good, but it seems that time is a commodity that compliance officers need more of

IT solutions

There is an increasing amount of software available to help companies streamline their payment-tracking processes, manage their sales forces, resolve their legal disputes, and adapt to new code provisions and updates across borders, but Dovletian says the question of what IT tools are available is just one aspect of the process. "There is a lot of software out there, but that's not really the issue. The issue is: have you stepped back and looked at all the silos and at what your infrastructure looks like generally?" she says. "Do you have a common language for information to flow into your system? Have you identified and connected with all the areas that should be feeding into your systems?"

Certainly, good technology is welcome; the better the systems, the better they can be audited readily and easily. Again, though, smaller companies can face challenges when it comes to equipping staff with the latest IT solutions. Eves says it would be "nice if staff had the means to access guidance in a way that would support decision-making in real time (e.g., via a tablet app for staff in the field). Having access to all the necessary information means that we would be supporting staff at the time since training will not necessarily cover every situation. Compliance often exists within a grey zone where there is not a simple black and white that can be covered in training."

At a technology-focused compliance event in 2014, one speaker—a vendor of IT solutions—pertinently reminded his audience that "IT solutions don't solve cultural problems." In Eigner's experience, however, a way to make these solutions work across cultures is "to present them as tools to make the business process more efficient rather than specifically a 'compliance tool.'" Then, he says, the level of acceptance is much higher, especially in countries that do not have direct transparency requirements.

Technology is all well and good, but it seems that time is a commodity that compliance officers need more of. Eves has faith in a patient, organic approach. He is confident that the EFPIA guidance on transparency and member state code changes are right and that, eventually, full disclosure will become the norm. "As an industry we need to work together to be sure there is consistency. The pick-up may be slow, but in time it will be accepted."

The same can be said about the CCO in pharma. PwC's State of Compliance Survey 2014 reminds us that the CCO role is only "roughly a decade old and has evolved rapidly." If it takes another 10 years for the CCO to become, as PwC predicts, "the c-suite star of 2025," it will still have been a fairly momentous rise to prominence, especially given the plodding pace at which pharma likes to advance. But, increasingly, as US healthcare lawyer Christopher Parrella wrote recently, "The chief compliance officer is viewed as the gatekeeper of a company's reputation." In this observation alone we can see the enormity—and importance—of the task ahead. PE

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Biosimilars Ramp-Up: Five Themes for the Future


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Steeped in controversy, biosimilars are finally coming to the US. Market entry, however, is still murky as legal decisions loom for first entrants. The strategic challenges are not new to companies affected by generic infiltration, but imitating substantially more complex molecular entities offers up a host of new operational questions.

By Casey McDonald

In-boxes and newswires filled up on March 6 with victory cheers, notes of caution, and, of course, ubiquitous calls for regulatory clarity. The historic moment: Sandoz, a generics division of Novartis, received the first-ever FDA approval for a biosimilar product, *Zarxio*.

The reference product is Amgen's *Neupogen* (filgrastim). The drug, which was originally approved in 1991 and still brings in north of a billion dollars for Amgen annually, is used to increase white blood cell counts in cancer and bone marrow transplant patients. It may no longer be a multibillion-dollar blockbuster, but *Zarxio*'s impact would be a symbolic knock to one of biotech's "old guard." A cursory reading of biotechnology's history would note *Neupogen* as one of its early revelations, no doubt enshrined in its Biologics Brand Hall of Fame.

As we stand, Amgen and Sandoz tease out a legal spectacle; on March 19, a federal judge denied Amgen's request for a preliminary injunction to stop *Zarxio*'s US launch. The case revolves around differing opinions on what must be disclosed in the "patent dance" of the Biologics Price Competition and Innovation Act (BPCIA). There likely will be an update (if not several) to this saga before this article goes to press.

The legal dispute is seen by many as a predictable step to delay the inevitable—roadblocks to buy Amgen another couple weeks, or possibly a fiscal quarter before competition begins to erode sales. Market entry is inevitable and likely will come this year. But for the remaining period, laws of big numbers apply. Weeks or months of sales for a billion-dollar drug still count for something.

Their arrival has been combative, but the time has come, and as many as three more biosimilars could get FDA nods in 2015. As we await the inevitable, *Pharm Exec* decided to examine five additional issues that warrant consideration.

1.) Levels of acceptance: Extrapolation, interchangeability, and switching

Zarxio, known in Europe as *Zarzio*, now has the FDA's OK for use across all indications included in the reference product's label. The "extrapolation" across all of the innovator drug's approved indications is one notable win for biosimilar makers. Running trials for each disease state would be costly.

The FDA's approval of *Zarxio* was quick and though it was expected, full extrapolation confirmed that the FDA is indeed "favorably disposed to having biosimilars in the market place," notes James Langley, chair of the Healthcare and Life Sciences Practice at The Mead Consulting Group.

A formal designation of interchangeability from the FDA will be another step as drugmakers, payers, doctors, pharmacists, and patients will contest a power struggle over whether a script can be transferred to the biosimilar and how.

Current state legislation for biosimilars (both passed into law and currently before various state legislators) regarding substitution, notification, etc., is widely varying. Some states may allow the pharmacist full discretion to make a substitution. Others might require notifying the physician before or after a change. Still others might only grant a substitution with physician's approval.

"Keep in mind that most debates around how substitutions will happen have made the assumption that biosimilars will gain interchangeability, but it's unlikely in the first year or two," says Langley. The FDA's 2012 guidance suggested that a company can apply for interchangeability, but it will be a high bar.

Biosimilar makers will go for one additional level of acceptance to be fully ingratiated into the marketplace—switching. Early on, only new patients will be put on biosimilars. Physicians treating patients with biologics are heavily concerned with immunogenic responses to the large foreign molecules floating in their patients' circulatory systems. Reactions are not generally responsible for severe adverse events, but they do mean that the immune system is saying it's had enough, blocking the treatment and greatly diminishing its therapeutic action. Likelihood of a reaction is already high, and lot-to-lot variation of biologic treatments concerns physicians as it is. Until switching studies can show that a

biosimilar does not raise the incidence of an immunogenic response, expect physicians to be extremely hostile to the idea of switching a patient who is being successfully treated by the innovator. For a good while, biosimilars will be limited to new patients.

2.) Some biosimilars might be better, others might seem better

The mindset surrounding biosimilars is that they will be a lesser version of the original. The argument made by those supporting biosimilar entry is that with solid manufacturing, they will be up to spec.

But in some cases, the biosimilar might be superior to the innovator product. This might fly in the face of some who see biosimilars as an inferior copy of the original. In comparison, how often is the cover version of a song better than the predecessor? This writer has always preferred the Isley Brothers' version of "Twist and Shout" to the Beatles'. Of course the flip side of that debate is "Hurt" by Johnny Cash.

The question comes down to variability, which is the whole reason we're sticking to the term "biosimilar." Biosimilars will vary from the innovator drug and, consequently, may have lower efficacy, greater safety concerns, and increased immunogenicity. But biologic therapies have considerable variation already. Biologics have variation from lot to lot; a fact that is at the core of working with biological systems and manufacturing complex molecules. Anyone who has worked with cell cultures knows how fickle they can be—with a slight humidity change, a different phosphorylation pattern results.

On top of lot-to-lot variation, physicians will speak of a perception of variation over time that exists. Statements like "2005 Humira is different from 2015 Humira" are not uncommon.

So who's to say that a biosimilar product won't vary on the side of slightly better levels of efficacy and safety rather than being slightly worse? No doubt these differences may be nearly impossible to determine as statistically significant in controlled trials.

But take heed. It's human nature to make judgments based on anecdotal evidence—doctors and patients included. Be prepared for case study "evidence" and trials of small numbers. Expect headlines saying biosimilar X is less expensive AND better! A headline like that could go viral.

"Physicians feel they will have a strong voice in the adoption of biosimilars, but most of the discussion in the industry to date has been about payer influence."

3.) Doctors dubious

"Based on the surveys we have done, physicians feel they will have a strong voice in the adoption of biosimilars, but most of the discussion in the industry to date has been about payer influence," says Mark Ginestro, a principal at KPMG, where he focuses on healthcare and life sciences. Some are choosing to be vocal claiming they should have a greater say.

But what they say is mixed. Speaking to physicians, you see some surprisingly divergent views on biosimilars, some being very open to use and others are much more cautious. This presents an "opportunity to differentiate products via communication to physicians," says Ginestro.

Clearly, advertising and education campaigns will be necessary for biosimilars, notes Joshua Cohen, research associate professor, Tufts Center for the Study of Drug Development. "Even if the FDA has done its job regarding safety, efficacy, and quality, there will be some skeptics," says Cohen. "There's a diffusion curve for any new product, and it will be hard to get early adopters. Some doctors will play a waiting game and look for more data on each biosimilar."

To "facilitate" doctor acceptance, there will no doubt be payer pressure using mechanisms like formulary exclusion. It will be challenging to force the issue on physicians, so expect payers to participate in educational programs, adds Cohen.

The loss of authority for physicians is nothing new, says Langer. Their greatest aversion, besides overall safety, concerns immunogenicity, which they fear will result from any kind of forced switching for patients already on the branded drug.

For now, the mindset is the same for physicians with biosimilars and biologics. When a patient is doing well on a treatment, don't change them. And once a response is lost due to immunogenicity, it is lost forever. New patients will be a different story.

Consider this: with the concerns over immunogenicity resulting from switching, won't doctors also be highly averse to switching from biosimilar and upgrading to the branded drug? Switching "up" or "down" could result in greater potential for immunogenicity. This factor makes biosimilars distinctly different from small-molecule generics, where a patient might try the generic and then bump up to the branded version to see if they can get a better result. With biosimilars, the initial decision will lock a patient into one therapy—at least until switching studies provide sanction.

4.) Trends driving acceptance—and the Sovaldi context

For the last few years, estimates for the likely range of price reduction for a biosimilar drug have been 25%-30% compared to the innovator product. So news out of Norway, that Orion Pharma is offering a 72% price reduction for *Remsima*, the infliximab biosimilar via the nations' tender system could

cause a "shock wave," according to Joseph Fuhr, Professor of Economics, Widener University. This could give other groups in the European Union and US the gumption to demand significantly greater reductions.

Generally speaking, the incentive to launch biosimilars in the US should be greater because companies can compete with greater discounts, notes Cohen. Price controls in Europe tend to keep the price of the innovator lower, and thus the percentage difference for the biosimilar is smaller. This is evident in Europe's generics market, which is less developed. This makes the tender offering by Orion all the more impressive.

Along with this potential shockwave, the conflagration over *Sovaldi* and resulting pacts that payers have made with hepatitis C virus (HCV) drugmakers make timing intriguing. Lessons have been learned; precedents have been set. Where a new drug enters the market in the same class as another drug, there is greater opportunity to negotiate and deeper rebates are possible.

Presenting at CBI's 10th Annual Summit on Biosimilars in late January, Langley pointed to additional driving factors that will incentivize lower-cost products. In addition to the HCV market as a primer, payers using formulary exclusions like the Express Scripts block will no doubt take advantage of biosimilars to cut out brands as cost-cutting measures.

Additionally, new payment system changes like accountable care organizations, bundled payments, and value-based measures will drive significant economic incentive to utilize lower cost products, says Langley. Other factor like hospital consolidation and integration of the full-care spectrum will demand greater cost per quality of patients' lives.

5.) Things will get complicated

Several regulatory issues remain, one being nomenclature standards. *Zarxio*'s approval came with a placeholder nonproprietary name, filgrastim-sndz, rather than certainty on the issue.

Hopefully this, and some other questions, will be answered once the biosimilars truly start to complicate markets. Five tumor necrosis factor (TNF) inhibitors is a complicated market already. But start wrapping your head around two or three, and eventually five or six, products for each molecule.

The markets will settle and saturate, notes Ginestro. He says manufacturers could enter markets in waves—maybe a few biosimilars to start with, then maybe another wave with lower-cost manufacturers. As pricing gets more aggressive, originator manufacturers may start pulling out.

"A 30% discount isn't the bottom," says Langley. As more products enter, you'll see more pressure on price, more negotiations with payers, and deeper discounts.

In spite of the confusing markets with low prices, several big Pharma and biotechs want in—Sandoz is a subsidiary of Novartis, Pfizer bought Hospira, and Amgen will have its own biosimilar wing, just to name a few. Big names ultimately confer manufacturing confidence with the consumer.

It will be important for these companies to seek balance, says Ginestro. Those that want to share in the biosimilar pie need to think about core competencies. Is innovation or operational excellence at the heart of each company?, asks Ginestro. Without clear divisions, an organization can end up with dual identities. It will be key that those hoping to do both keep biosimilars efforts from impacting their innovation engine, Ginestro stresses.

Timing into markets could also be key. Unlike with innovator drugs where "first to market" can be crucial, biosimilars may see a second-mover advantage, notes Fuhr. Sandoz is taking the brunt of costs not just battling the innovator company in courts but also navigating the nebulous FDA. It will be interesting to see if Apotex's pegfilgrastim can enter the market using benchmarks set by Sandoz. Depending on how delayed Apotex's biosimilar is, there could be substantial time for Sandoz to earn its investment back, but it could also absorb extra cost educating the market for their competitors' benefit.

But considering the many complexities and the potential massive systemic cost savings, can anyone blame FDA from taking its time for further guidance? Rather be late and right, than early and wrong. PE

Casey McDonald is *Pharm Exec*'s Senior Editor. He can be reached at cmcdonald@advanstar.com.

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Pharma Pricing: Striking a Post-ACA Balance

Making sense of the new cost-containment model and value-for-money conundrums like those in the HCV space

Even as evidence grows that we have begun to bend the US healthcare cost curve and reduce the inexorable rise in national healthcare expenses, there is a lot of talk about pricing, particularly pharmaceutical pricing. For pharmaceutical executives, engaging in this conversation is long overdue. Healthcare pricing poses a potential threat because people may get priced out of the market. And it's not just drugs and medical devices, but pricing for medical procedures, physician visits, and hospitalization are also under scrutiny.

How the ACA affects costs

The goal of the Affordable Care Act (ACA) was to slow the rise in the overall cost of healthcare and expand health insurance coverage to more Americans. Constraints on costs are expected to come from three primary market forces. First, broadening insurance coverage enlarges the risk pool and gets healthcare services to uninsured people before their illness gets too serious (and expensive).

Secondly, by moving from a fee-for-services model to a pay-for-outcomes model, the financial incentives for healthcare providers shifts to quality and coordinated care to keep people healthy and out of the hospital. Finally, as consumers begin to bear more of the direct cost of insurance and out-of-pocket co-pays, there will be additional pressure on pricing.

In our free-market economic system, we've been reticent to tell private-sector producers of products or services what they can sell a product for, leaving it to customers and competition to rationalize pricing. The ACA largely left drug pricing to the market, assuming supply, demand, transparency and outcomes data would identify the right price ranges for most products.

The value has to be measurable—pharmaceutical products will need to justify their price with outcomes data

Pay now or pay later

However, healthcare is a special case. Unlike most consumer products and services, healthcare is rarely a discretionary purchase. We either buy health services (e.g., physician office visit, lab test, drug therapy) today when we need it—when it is the most effective to treat or cure—or we, or society-at-large, will ultimately pay for it later when the situation is likely more acute and the cost of treatment is much higher. It makes sense that we do whatever we can to offset that higher risk tomorrow by providing access to health services today.

Offsetting future financial risk requires two inputs—universal access and measurable quality. We need to cover as many people as we can to insure that everyone has adequate access to healthcare products and services—but not just any products and services. Patients need access to quality care that results in positive outcomes.

A business model transformation

In this model, insurers provide the universal patient access and providers and pharmaceutical, diagnostic, and device companies deliver the quality outcomes. However, the financial lubrication in this complex workflow will require a new approach to balancing cash flow between healthcare entities. In fact, we are in the middle of a massive restructuring of risk, payments and health accountability.

With the introduction of universal insurance coverage and new incentives for cost containment and improved health outcomes, the ACA disrupted the long-standing business model that governed cash flow and profitability among the various healthcare entities.

The ACA has forced the national conversation to shift from one about pricing to one about value. When you really unpack the philosophy behind the ACA, it is a philosophy of value: *We're going to pay for outcomes, not just for procedures or services.*

Is value-based pricing the answer?

Framed as value, the question then is about efficacy. Whether it's a pharmaceutical therapy,

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hospital stay, or a medical procedure, did it fix the problem? Did we get the kinds of long-term, healthy outcomes we're looking for? And if so, if we're able to reduce hospitalization or arrest a chronic decline in health, then the result—the value of costs saved and future productivity secured—should be factored into the acceptability of the price of achieving this outcome.

But the question remains, is there a price point that is unacceptable, regardless of the long-term value?

Do cures deserve a premium price?

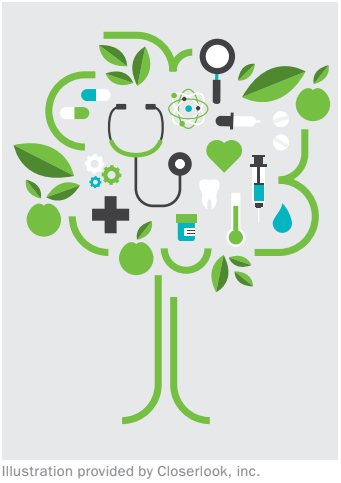
Gilead's *Sovaldi* has become a lightning rod for this discussion. *Sovaldi*, which can cure hepatitis C virus (HCV) for 80% to 100% of patients who take it, carries a retail price of $84,000 for a 12-week regimen. Private payers, states insurers, and Medicare and Medicaid are up in arms at the cost. Hence, the moves by the major pharmacy benefit managers (PBMs) to cut exclusive deals with the makers of the new HCV drugs in exchange for discounts.

But on the other hand, Sovaldi is curing people, which very few drugs actually do. Compare the long-term cost of someone who has HCV, who will be on drugs and in and out of the hospital for the rest of his or her life, to a short-term spend of $84,000, and you'll recognize that while there's certainly short-term pain, there's huge long-term value.

We either pay for it now or we pay for it later. It becomes a time-value of money question.

The time-value of money

Insurance companies were built on an actuarial model of paying for chronic illness over time.



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There hasn't been a financial scenario that assumes there is a cure that will end treatment costs for a chronic illness, short of death. Insurers are accustomed to paying relatively smaller bills over long periods of time, not a large one-time payout.

However, if you step back from the intimidating numbers of three million HCV patients at a cost of $84,000 per patient and consider the literature that predicts treating the old way is on a path to rise from $30 billion a year to $85 billion a year over the next 20 years (complications, liver transplants costing more than $550,000 each), and that the number of new cases of HCV is falling (now only 20,000 new patients annually), not even taking into account the quality of life and productivity of those cured citizens, there is an actuarial risk/financial model that makes sense, even at a high short-term cost.

Total cost of ownership

As healthcare leaders, we need to reframe this argument in terms of total cost of ownership. There is a total cost of health in this country, and if by investing in innovative solutions today we can improve long-term cost and wellness tomorrow, then that is a move that makes sense.

The technology industry held a similar conversation 20 years ago when software and hardware manufacturers like Microsoft and IBM introduced the concept of total cost of ownership to chief information officers (CIOs). While the initial costs to outfit your entire company with IBM computers or a new Microsoft operating system might be high, if you looked at the total cost of ownership of that technology amortized over three to five years and analyzed the improved productivity and lower maintenance costs from the investment, it was actually quite affordable.

We need to look at healthcare in a similar fashion. We need to factor in the total cost of ownership—the total cost of the therapy and procedure and the total outcomes benefits—before we take severe measures like restricting access to certain types of care based on price or introducing price controls on pharmaceutical companies.

Amidst the feverish debate over pricing in healthcare, the industry needs to focus on the value that healthcare can provide to patients and let that calculation dictate relative costs. The value has to be measurable—pharmaceutical products will need to justify their price with outcomes data—but that's part of the enlightened conversation that will lead to a more rationale social and economic contract between healthcare suppliers, providers, patients, and payers. PE

Pharma Distribution Deals Raise Concerns

Does patient choice matter to antitrust enforcers?

A phenomenon is beginning to take hold in pharmaceutical distribution. Large pharmaceutical benefit managers (PBMs) such as Express Scripts Inc. are beginning to use their heft to strike exclusive drug deals in order to lower the cost of healthcare.

Consider Express Scripts' recent negotiations over a hepatitis C treatment with suppliers, AbbVie and Gilead Sciences. Express Scripts offered AbbVie an exclusive distribution deal in return for a lower price for their drug, *Viekira Pak*—the list price of which is approximately $84,000 for a 12-week regimen. Once the exclusive deal was reached, Express Scripts dropped Gilead's competing hepatitis C treatment, *Harvoni*, which has a list price of approximately $95,000 for a 12-week regimen, from its coverage options. Thereafter, Gilead reached an exclusive deal for *Harvoni* with Express Script's competitor, CVS Caremark, also reportedly at a substantial discount. If passed on, the savings achieved from these exclusive deals will help lower health plan costs and, ultimately, the costs of health insurance premiums for the average Joe.

However, these exclusives, as many pharmaceutical manufacturers have pointed out, can also limit patient and physician choice. We must keep in mind that patients' medical history and unique body chemistry is critical when considering treatment options, and prescriptions may not be easily substituted. Indeed, if the Express Scripts-managed patient has an adverse reaction to its only contracted drug of relevance—in this case, *Viekira Pak*—the patient can suffer substantial harm. Moreover, if the excluded drug is more effective for particular patients, as may be the case where the drugs are not exact bioequivalents of one another, the exclusion will cause patient harm as well.

To be sure, exclusive contracts between pharmaceutical concerns and PBMs raise significant public policy issues. And while they can be procompetitive—particularly where substantial cost savings are achieved, they can potentially violate antitrust law. The following articulates the antitrust principles that govern an analysis of these arrangements.

Exclusive deals are generally procompetitive

There are many types of exclusive deals in our economy. The vast amount of them are procompetitive, inasmuch as, in most cases, neither of the parties to the deal have enough economic heft or market power to impact competition adversely. Consider an exclusive distribution deal between a local pizza parlor and a mozzarella cheese manufacturer. If the markets for pizza making and mozzarella cheese supply are competitive, as most likely is the case, the exclusive arrangement would not be able to cause the market-wide price of pizza to increase or the overall output of pizza to be reduced. Neither would these exclusive deals harm competitive mozzarella suppliers from contracting with alternative pizza parlors for distribution. The exclusive in this instance will lead to lower cost for the parlor and lower pizza prices, which benefit consumers.

To determine whether the Express Scripts/AbbVie or any distribution exclusive is anticompetitive on the whole, one must balance the demonstrated anticompetitive impacts of the exclusive with the cost savings that are generated by the deal

Some pharmaceutical distribution exclusives may be anticompetitive

However, not all exclusive deals are procompetitive. If an exclusive arrangement prevents substantial numbers

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Photo: Thinkstock

of customers from purchasing that product, particularly when certain customers prefer a product's unique characteristics, then the arrangement is anticompetitive. This can occur when one of the entities wields market power.

Express Scripts has control over the drugs that are ultimately dispensed to approximately 100 million Americans. These patients are unable to fill prescriptions for drugs that Express Scripts refuses to cover, unless, on appeal and after substantial administrative burden and delay, they are able to convince their insurance company to do so. If a patient prefers Gilead's treatment—even if the cause is medical, like less side-effects—he or she will likely not receive it without jumping through the hoops of the insurance company bureaucracy.

To determine whether the Express Scripts/AbbVie or any pharmaceutical distribution exclusive is anticompetitive on the whole, one must balance the demonstrated anticompetitive impacts of the exclusive with the cost savings that are generated by the deal. In the context of the Express Scripts/AbbVie exclusive, Express Scripts apparently saved thousands of dollars per regimen for hepatitis C treatment. If these cost savings are passed on to end consumers rather than pocketed by Express Scripts, the deal would have substantial procompetitive aspects. This suggests that these deals do not violate antitrust law.

Will antitrust enforcers scrutinize exclusive pharma distribution deals?

The trend towards pharmaceutical distribution exclusives seems to be gaining momentum. Express Scripts CEO George Paz, for example, has specifically stated that the company may seek to exclusively contract with either Regeneron Pharmaceuticals or Amgen over their new class of cholesterol-reducing biologics called pro-protein convertase subtilisin kexin 9 (PCSK9) inhibitors.

The question must be raised, therefore, over how likely it will be that antitrust enforcers challenge these deals in court. In this writer's opinion, most of these deals will likely not be challenged even if PBMs such as Express Scripts are a party to them. Our antitrust authorities, particularly the Federal Trade Commission, normally pursue cases that concern practices that increase healthcare pricing, not those that decrease them.

This does not mean, however, that certain exclusive pharmaceutical deals would not be subject to meritorious attack, particularly where the exclusion causes a substantial and adverse medical impact on a large patient populace. In that scenario, even if public enforcers do not seek to enjoin the exclusive, there is a good chance that the excluded competitor, who would suffer substantial losses, may "fill the breach" of any government effort to litigate such cases. PE

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HEALTHCARE & LIFE SCIENCES REVIEW

MEXICO

BRINGING ENERGY TO HEALTH

While the recently-approved energy reform might have taken much of the international spotlight, there is much more going on in Mexico today. The recent structural reforms undertaken by Peña Nieto's government have one objective: restarting the engine of growth. The pharmaceutical industry is no exception to this. With a regulatory authority risen to become a reference in the region, a healthcare reform under way and cost-competitive manufacturing, the pharma sector in Mexico is paving the way to fuel future growth, for local and international players alike.

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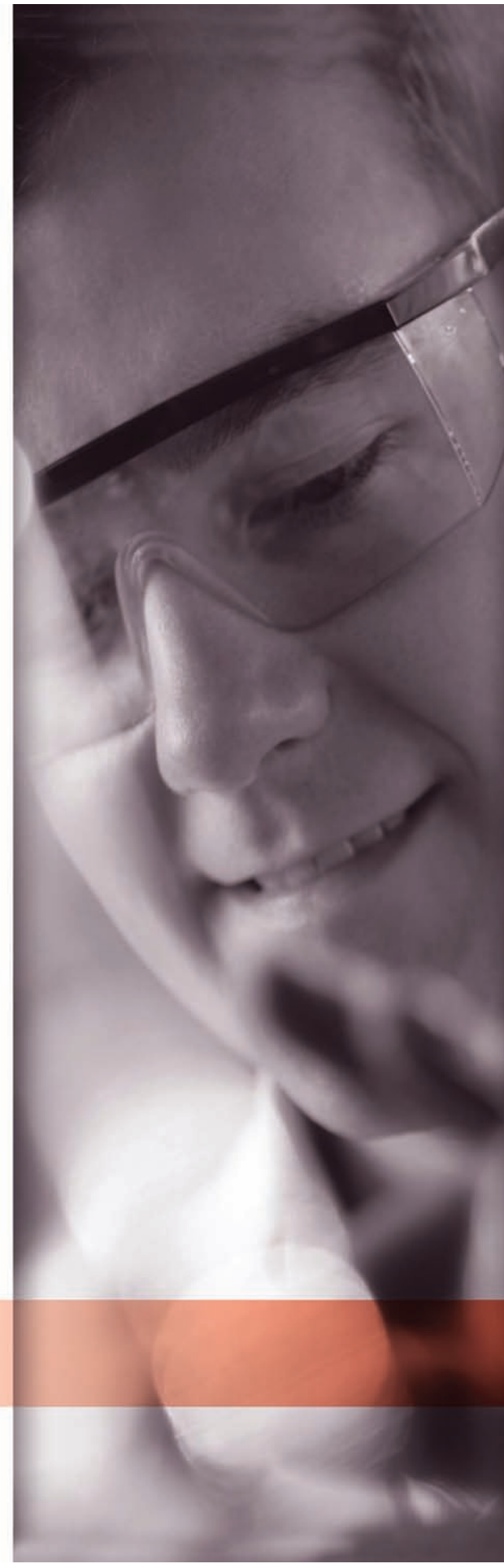

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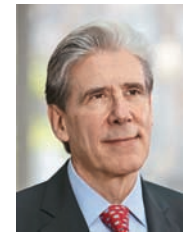
READY, STEADY, GO!

While the global investment community has been eagerly following the developments of the BRIC (Brazil, Russia, India and China) block, Mexico has been silently paving the way to fueling future growth. Few emerging markets can boast a reform agenda as ambitious as Mexico's. Since he took office in December 2012, besides opening the long-time state-run energy sector to foreign investment, Enrique Peña Nieto's government has undertaken an unwavering program of reforms aimed at cutting Mexico's chronic levels of tax evasion and spurring competition in sectors heavily dominated by oligopolies such as telecommunications, broadcasting and banking. The objective: restarting the engine of growth. And the efforts are apparently starting to pay off. After the slump experienced in 2013 and a modest 2.1 percent increase in 2014, GDP growth is forecasted to pick up to a more encouraging annual average between three and four percent in 2015-19.

The outlook must come as a breath of fresh air for companies operating in Latin America. After a rough 2014 plagued by high inflation, economists expect a gloomy year for Mexico's big regional rival, Brazil, whose GDP is forecasted to shrink by 0.5 percent in 2015. Colombia, Chile and Peru are feeling the strain of the slackening commodity boom of the last decade, while Argentina and Venezuela suffer from chronic stagflation.

Mexico, on the contrary, presents a relatively stable economic, political and business environment that, under the influence of the recent structural reforms undertaken by Peña Nieto's government, offers a much more encouraging panorama. As Ugo de Jacobis, president and general director of AstraZeneca Mexico points out, "Regardless of the changes the country is undergoing, the level of certainty it provides – especially from an economic perspective – is higher than in other countries in Latin America. Competition is fierce, but the market as well as the regulatory framework in place provide the necessary certainty to keep investing in Mexico."

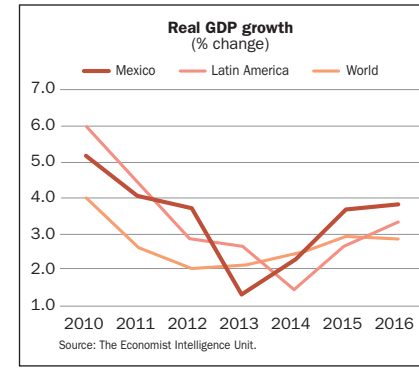
From left: Mikel Arriola, federal commissioner of COFEPRIS; Julio Frenk, dean at the Harvard T.H. Chan School of Public Health; Enrique Ruelas, former president of the National Academy of Medicine; Guillermo Soberón, former minister of health

FROM VOLUME TO VALUE

Healthcare is one of the next items on President Peña Nieto's busy agenda. The objective: moving Mexico towards universal healthcare coverage. The initiative was started at the beginning of 2000 by the previous government with the objective of ensuring in the long term that "any Mexican – employed or unemployed – could go anywhere in the country and get quality healthcare at any institution," explains Maki Ortiz, president of the Health Commission at the Senate.

Historically, the Mexican health system has been fragmented among different providers and access to healthcare services was only offered to salaried workers and their families. At the beginning of 2000, the two main public healthcare providers – the Mexican Institute for Social Security (IMSS) and the Institute for Social Security and Services for Civil Servants (ISSSTE) – hardly covered half of the population, leaving nearly 50 million Mexicans uninsured. Since then, Mexico has gone a long way towards the creation of a universal healthcare system. The first important milestone was laid in 2004 with the launch of *Seguro Popular*, a public insurance scheme offering previously uncovered Mexicans access to a package of basic health services. A decade after its implementation, national commissioner Gabriel O'Shea announced proudly that: "57.3 million previously uninsured Mexicans are now enrolled in *Seguro Popular*."

"When [...] *Seguro Popular* was approved a decade ago, we were aware that this was a mid-term reform and that the next step was the integration of the public institutions providing healthcare services in Mexico and the possibility of interaction with private care providers," comments Julio Frenk, former minister of health and currently dean at the Harvard T.H. Chan School of Public Health. After universal enrollment – today almost completed – the next step is universal coverage, which means access to a package of comprehensive healthcare services with financial protection. This is the stage Mexico is currently moving towards. As a matter of fact, over ten years the number of interventions covered by *Seguro Popular* has increased threefold, the amount of drugs included more than 300 percent, and the number of diseases included in the so-called fund for protection against catastrophic expenditures has been raised from four to 59. The last step would be universal effective coverage, which implies services are provided with a level of quality that ensures a successful effect on the patient as well as on society. Because as Enrique Ruelas, former president of the National Academy of Medicine, points






From left: Hector Valle, former general manager for Northern Latin America at IMS Health; José Campillo, president of FUNSALUD; Maki Ortiz, president of the Health Commission at the Senate; Gabriel O'Shea, national commissioner of Seguro Popular

out, "universal health coverage is about value, not only volume. If you don't introduce quality to the equation, you risk doing more harm than good."

The upcoming reform aims at creating a universal healthcare system under the concepts of portability of services and convergence. The idea is to give Mexicans the opportunity to use healthcare services at any institution, independent of their affiliation – a measure already approved for obstetric emergencies a couple of years ago to face the dramatic number of maternal deaths in the country. This will soon include a limited number of chronic-degenerative diseases, such as heart failure, diabetes, kidney transplants and HIV, among others, before moving on to cover more diseases over time. "Three main institutions cover more than 90 percent of our population: if we let people choose among those three options through universal healthcare coverage, this will lead to a healthy competition to see who can provide the best service. I see that as something extremely positive that can take our health care system to a whole new level," comments Guillermo Soberón, former minister of health.

However, a number of challenges stand in the way towards effective implementation of universal coverage. First, universal enrollment: while the Ministry of Health claims that full coverage is almost reached, Hector Valle, former general manager for Northern Latin America at IMS Health, argues that "studies carried out by IMS Health, the National Public Health Institute and the National Institute for Statistics and Geography (INEGI) indicate that around 20 percent of the population is still uncovered." Second, healthcare expenditure. Over the last decade, despite the number of Mexicans enrolled skyrocketing, total expenditure on healthcare increased from 6 percent to just 6.2 percent, well below the average 7.4 percent of other Latin

American countries and the 9.3 percent average of OECD countries; on top of this, nearly half is still paid directly by patients. Additionally, the Ministry of Health recently announced a cut of nearly USD 650 million to the health budget, probably a consequence of the steep fall in oil prices, which is forcing many oil-producing countries as Mexico to review their federal budgets.

A further hindrance is effective integration of different healthcare providers. "The systems and processes they are using today are completely different and separate. If you want to build an integrated system, you first have to standardize and connect the existing ones – something which is not happening yet," points out Valle. Last but not least, as José Campillo, president of the Mexican Health Foundation (FUNSALUD) argues, "we support increased participation of the private sector in the health sector through outsourcing of services and public-private partnerships. But there are still many questions about how this should happen."

The concrete methods to achieve effective integration, critical to create a working universal healthcare system, may still remain undefined; however, undoubtedly Mexico is moving in the right direction.

RAISING THE BAR

Creating the conditions to drive growth in the pharmaceutical sector has been the top priority of Mikel Arriola, head of the Federal Commission for the Protection against Sanitary Risk (COFEPRIS) and undisputed regulatory star of the sector. "I have always been firmly convinced that having an efficient and transparent authority could only generate growth in the industry you regulate," he notes. And since his appointment, back in April 2011, he has been walking the talk. Besides catching up on the backlog of 25,000 drug registrations left behind by the previous administration, the commissioner has pushed to cut the timeframe to authorize new medicines

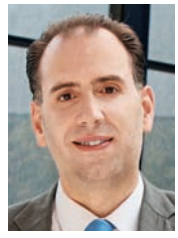
A roadmap to the healthcare reform

José Alarcón Irigoyen, partner and leader of the Healthcare Practice Mexico and Hispanic America, PwC

The government announced its intention to move towards a universal healthcare system. How do you envision this upcoming reform?

We think the government has three ways to go: first, an evolutionary approach, whereby it will create a portability platform by disease to incorporate financing, electronic patient record and the right to choose the health provider depending on the disease. Second, an innovative approach fostering public-private partnerships not only for large high-specialty hospitals, as it is the case today, but taking it to the next level. The Mexican Health Foundation (FUNSALUD) is very much involved in this kind of projects and is trying to move the Mexican healthcare system in this direction. A third way would be a revolutionary approach, as it was the case for Mexico's state oil company Pemex; in the case of health it would be by separating the different elements of the sector, i.e. regulation, financing, provision and management.

So far a high degree of political capital was already used to move forward other relevant reforms passed by the government, so we think that currently the main obstacle to the implementation of the reform is getting a consensus among the main players of the sector, including trade unions. We may see an evolutionary approach during the administration of current president Peña Nieto to slowly move by 2018–20 to a revolutionary approach, once the government has tested it can work and has clear examples and benefits.

From left: Rafael Gual, general director of CANIFARMA; José Alberto Peña, vice president and general manager of GSK

on the market from 360 to 60 days.

But there are other jewels on the crown of Mexico's revamped regulatory authority for Arriola to boast about. The first is the long awaited recognition by the Pan-American Health Organization (PAHO) as a national regulatory agency of regional reference in July 2012. "The recognition was a milestone, because today drugs registered with COFEPRIS are recognized at international level. And this has helped local companies start exporting to other countries, especially to markets in Central and Latin America," explains Socorro España Lomelí, executive director of ANAFAM, the association that brings together local drug manufacturers. The second milestone came in June 2014 with the recognition by the World Health Organization (WHO) as a functional agency for vaccines for the 2014-17 period, which adds Mexico to the elite group of 28 players in this segment. "Taking into consideration the fact that only a limited number of countries worldwide have this recognition, it's definitely something Mexico can be proud of," acknowledges José Alberto Peña, vice president and general manager of GSK Mexico. "This recognition will allow the market to attract more local manufacturing to strengthen internal consumption but also position Mexico as an exporting country."

"The recent reforms ensure the country offers today very different conditions for investment," points out Arriola. "At COFEPRIS we have included an added value, which is untouchable but very important: predictability and transparency." And the industry seems to welcome a stricter regulatory authority complying with international standards. Having raised the bar, now the priority of the industry seems to be getting the recognition it deserves. According to estimates of CANIFARMA, the national chamber of the pharmaceutical industry, today the sector represents 1.2 percent of Mexico's nearly USD 1.4 trillion GDP and 7 percent of the manufacturing GDP, second in importance only to the buoyant automotive sector. Rafael Gual, general director of CANIFARMA, has made it his personal objective to transform the pharmaceutical industry into the most important manufacturing sector in Mexico. "Besides the numeric objective, what is important is that we are working closely with the government to ensure the pharmaceutical sector is recognized as an increasingly important player in the economic development of the country," he notes.

The recognition of the national pharmaceutical industry as a key sector for Mexico's economy and population is also acknowledged by Socorro España Lomelí, executive director of ANAFAM, as one of the challenges of the association. "Mexican drug manufacturers are investing in the country and are fighting for it – and this should be recognized at national and international level." Alfredo Rimoch, general director of Liomont, one of the top Mexican players, shares this point of view: "the Mexican pharma industry is a strategic sector and does not get enough help from the government. We don't want government protection; we want support and those opportunities and incentives that are promoted by the government and granted to other industries, such as the automotive, and we still do not receive."

BioGraft: a tissue bank made in Mexico

José Raúl Flores Fletes, general manager Biograft

BioGraft is something of a rare breed in the Mexican biotech landscape. As José Raúl Flores Fletes, founder and general manager, likes to put it, his company is an exception in Mexico. "We are an innovative, young and paradigm-breaking company." BioGraft is a biomedical technology firm with a very special focus: implants derived from human muscle skeletal tissue. Back in 2003 Flores identified a growing need for these devices in the Mexican market, which often only had poor quality or even smuggled products. Quality was number one priority from the very beginning, so Flores decided not only to comply with local but also with international regulation, undergoing the audits of the US Food and Drug Administration (FDA) and registering it with the American Association of Tissue Banks (AATB).

Paradoxically, the main challenge the company had to face was in the local market: widespread skepticism towards the *Hecho en México* (Made in Mexico) brand. "Locally manufactured products suffered from a very poor image because of low quality standards," Flores explains. "To overcome this negative perception we decided to implement an open house policy, whereby we invited the surgeons to visit our facilities and see how we produce our implants." And he seems to have won his bet: today some of the most important key opinion leaders in traumatology and orthopedics in Mexico are using BioGraft's products.

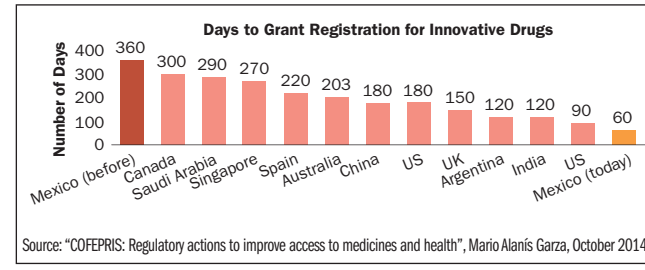
Today the company is not only consolidating operations on the local market, but also already exporting to South Korea, Spain, Switzerland, Guatemala and Peru, as well as eyeing the challenging German market. A success story, which is also possible partly thanks to the support from the National Council of Science and Technology (CONACyT), Mexico's entity in charge of promoting scientific and technological activities. The next step is entering the segment of cadaveric skin derived implants, which is seeing an increasing demand. But Flores' ambitions go far beyond that: "In five years I'd like to see BioGraft as an engine of a biotech cluster, having a more international presence, leading the Mexican association for tissue banks and being finally recognized by the skeptics."

MEXICO: A MATURE PHARMERGING MARKET?

From left: Socorro España Lomelí, executive director of ANAFAM; Alfredo Rimoch, general director of Liomont

Almost ten years have passed since IMS Health listed Mexico – along with China, Brazil, Russia, India, Turkey and South Korea – among the seven 'pharmerging' markets promising above average prospects for growth. All markets shared common drivers such as an increasing government healthcare investment, a high level of out-of-pocket expenditure and an increasing burden of chronic diseases. Today Mexico is still viewed as an emerging market in terms of dynamics, but with growth rates that better resemble those of mature economies.

"Many companies typically classify Mexico as an emerging market, although it is actually behaving as a mature one," points out Miguel Salazar, president and country managing director of the family-owned German company Boehringer Ingelheim. Pedro Galvís, managing director of another important German player in Mexico, Merck, shares the same view: "Despite being considered an emerging market, Mexico resembles a mature market in several aspects. It's a double-edged sword sometimes, because expectations from headquarters are high as Merck Mexico grows at a double-digit rate; however, the market does not." Besides growth rates, an increasing participation of the government is also impacting performance, as "we are witnessing a trend towards switching out-of-pocket and retail to a more institutional market," adds Galvís.



Source: "COFEPRIS: Regulatory actions to improve access to medicines and health", Mario Alanís Garza, October 2014.

According to IMS Health, by the end of 2013 the pharmaceutical market in Mexico was worth nearly USD 15 billion, with a compound annual growth rate of approximately 6 percent in the 2009-13 period, but only a modest 3 percent growth in 2013 and less than one percent in 2014. While of-


From left: Miguel Salazar, president and country managing director of Boehringer Ingelheim; Pedro Galvís, managing director of Merck

fering opportunities from an ageing population, a changing epidemiological profile and expanded healthcare coverage, the market also feels the strain of several factors, which include the government's push to drive down prices, an increasing penetration of generics and, consequently, diminishing brand loyalty among consumers. Moreover, the fiscal reform implemented at the beginning of 2014, combined with the annual inflation breaking the four percent ceiling set by Mexico's Central Bank, hit consumers' purchasing power – all important changes in a market where nearly half of the health expenditure is out-of-pocket.

Since 2012 the government has made it a priority to improve the access of the population to a well-supplied drug market that offers medicines at the most affordable prices. Aligned with this policy, the regulatory authority implemented a strategy to facilitate the approval of generic drugs. Since then, 31 active substances have entered the market and 287 new generic drugs were registered, dramatically increasing generics penetration. Today, with an 84 percent volume share, Mexico is the second market in the world for penetration of generics behind the US.

"The whole pharmaceutical industry has done a lot to inform patients about bioequivalence, to make sure they understand that a generic drug is the same as an innovative one and that they represent a cheaper option for treatment," explains España Lomelí of ANAFAM. "People's mindset towards generics has been changing and an increasing number of Mexicans are now aware that generic products are just as good as brands," points out Andrés Aguirre, strategy director of Grupo Bruluart. "Sometimes it is also a matter of not having a choice. When people cannot afford to buy branded products, they try generic versions only to realize they work just as well. This means that from that moment onwards, branded products are not an option anymore," adds his brother Juan José, sales director of the group.

So it comes as no surprise that, despite the meager overall market growth in 2014, local, mainly generic-driven, players have showed the best perfor-

Family firms in transformation

The relatively stable market growth of Mexico in recent years has lured new players into the pharmaceutical market, where ProMéxico estimates that almost 700 companies compete today. A higher degree of competition indeed forces local, especially family-owned, companies to implement changes to adapt to the new landscape and stay competitive.

Juan José Aguirre, sales director of Grupo Bruluart

Andrés Aguirre, strategy director of Grupo Bruluart

Grupo Bruluart has been in operations for more than 60 years, yet it was only in 1971, when the Aguirre family, today at the head of the group, took over the administration. The rollercoaster of the first years driven by more stringent marketing regulations and the economic crisis Mexico went through in the early 1980s, belongs to the past. Today the company can boast a sound positioning in the market: the group relies on two manufacturing facilities in the State of Mexico, its own distribution branch Brudifarma as well as a pharmacy chain, Farmacia GI. "We have just been through a three year period whereby the company has been shifting from a traditional family business with our father as a single head giving the guidelines to all sections of the firm, to a more corporate organization with a board of advisors," explains Juan José, sales director of the group. "We are still a family owned business with our father as the chairman, but we are definitely empowering each individual general manager more." "What we have noticed is that, since we have both taken up our roles within the company at a full time, the collaboration between different sections of the company has improved drastically," adds brother Andrés, strategy director of the group. "We often see family businesses getting lost when the company is being transitioned to the management of the next generation. However, we have been very lucky because besides having a very open-minded father, who is happy to let go of today's decisions, we have very different personalities that allow us to complement the needs of today's changing industry."

Sandra Sanchez y Oldenhage, deputy general director of Probiomed

Probiomed, on the other hand, is going a different way. Founded back in 1970, the company has been family-run ever since, moving from the API segment into generics and, eventually, becoming the first Mexican company to venture in the biotech segment. Today, strong with a portfolio of products exported to 14 countries as well as four production plants, the founder and current president of the company, Jaime Uribe de la Mora, wants to move Probiomed to the next level, and to do so has appointed general director Sandra Sanchez y Oldenhage, a young professional with more than 20 years in the industry, and former general manager of Amgen Mexico. "As general director I have a three-fold mission: institutionalize the company – establishing and enabling corporate governance – expand it internationally and drive organic growth with in-market products and the development of new drugs," she explains enthusiastically. The vision: to become the global biosimilar company from Mexico to the world. "This strategy will allow the family business to accelerate growth in a disciplined manner, maintain competitiveness and ultimately become a strong global player in a rapidly changing external environment. An environment where you need to reinvent yourself to ensure you can endure the challenges and boldly harness the opportunities."

mance in the retail market, with a more than 6 percent year-on-year increase. Large product portfolios, volume-driven agreements, integrated distributors and strong bounds with the public sector help them outpace big pharma.

ACCESS IS THE NAME OF THE GAME

So, given the skyrocketing increase in the penetration of generics, where does innovation come into the equation? Apparently it's a common concern for big pharma. "Ensuring that new products get to end consumers is one of the biggest challenges that we are facing as an industry at the moment," points out José Alberto Peña, vice president and general manager of GSK Mexico.

According to an IMS Health study carried out in 2014, in Mexico it takes up to 4.3 years for a new treatment to be listed in the public healthcare sector, compared to two years in the UK and Japan, and 3.4 years in Brazil. "Drug access at Mexican public healthcare institutions is currently the main issue for all multinational companies," explains Pedro Galvís, managing director of Merck, "I think this is where both the opportunities and challenges lie. The government has made important efforts to expand coverage to the over 112-million population and this makes us optimistic. But we are still far from being a country where people have access to medical innovation." Again, COFEPRIS has taken important steps over the past years in order to improve the situation, also including innovative drugs in its access strategy. Whereas in 2010, before the Arriola administration, only three new molecules were approved, "between March 2011 and August 2014 we have issued 133 new molecules, which account for 20 different therapeutic classes that represent 73 percent of the mortality causes in the Mexican population, namely chronic diseases," points out the federal commissioner. "Moreover, we are now authorizing new drugs within 60 working days, which has helped transform Mexico into the global launch country for four new molecules (two for asthma and two for diabetes) and the dengue vaccine."

Alas, the problem does not lie within the regulatory authority. After a drug gets the approval from COFEPRIS, it still has to pass the General Health Council to later be approved through each and every one of the healthcare providers, i.e. IMSS, ISSSTE, *Seguro Popular*, the Army, the Navy, etc.

Cristóbal Thompson, executive director of AMIIF

Upon his appointment as executive director of AMIIF, the association bringing together the most important research-based pharmaceutical companies, Cristóbal Thompson, made it his "personal mission to move AMIIF from being a stand-alone organization which only represented the interests of its members, to being one integrated in the healthcare sector and a meaningful actor able to sit down with the government to discuss how to improve the health system as a whole." The result of this effort is a document called 'AMIIF 2024', which pictures the Mexican health system in ten years. "We realized that if access was the most important problem, we needed to start addressing it," he continues.

Alexis Serlin, country president of Novartis

"Especially in the case of non-communicable diseases, waiting times are unacceptable for patients and make the country lose competitiveness. Even though Mexico is the 13th largest pharmaceutical market in the world, why should a chairman consider it a priority if access is not granted? Today access is the name of the game."

To find a trade-off between innovation and affordability, drug makers are increasingly looking for a collaborative ap-

UDIMEB: When academia meets pharmaceutical R&D

Sonia Mayra Pérez Tapia, executive director of UDIMEB

When in the 1970s Sergio Estrada-Parra, today one of the most renowned immunologists in Mexico and winner of the 2012 National Science Award, started working on transfer factors at the National Polytechnic Institute (IPN), he probably did not imagine what would be the future of this project. Almost 50 years later, the immunomodulatory drug result of his research is registered and marketed under the brand Transferon. Yet, what started as a pure academic research project developed into UDIMEB, a spin-off which brings together different activities with one common denominator: R&D. "Today UDIMEB is a three-armed institution which comprises UDIBI, a national laboratory unit offering R&D bioprocess services to the private industry and the academia; USEIC, an institution providing free clinical services in the field of immunology and alternative treatments based on transfer factors to more than 20,000 patients," explains Sonia Mayra Pérez Tapia, today executive director of the organization. "Last but not least we have FARMA FT, the company in charge of manufacturing the immunomodulatory drug Transferon."

With UDIBI the organization is meeting the increasing demand from the local pharmaceutical industry for specialized R&D services to complete the development of their products. "Today, the private industry comes to UDIBI in search of specialized help to complete their developments in the fields of pre-clinical tests." The executive director has ambitious plans for UDIMEB. "Our dream is to be able to offer to the industry basic R&D, proof of concept, pre-clinical and toxicological tests and, eventually, Phase I studies for clinical research, with the necessary equipment and infrastructure to perform them in-house." Alas, the horizon is not cloudless. In order to beef up strategic partnerships with the private sector, it would be easier for UDIMEB to spin off to become an autonomous business. However, Mexico's cumbersome regulation for public education institutions hinders this. "Mexico is the only country where private-public collaborations are seen as 'prostituting' science," she regrets. "I think initiatives, which bring together private industry and academic institutions should be strongly encouraged."

proach with the government. "Drug access is a shared responsibility between the private and public sector. Fortunately the collaboration with the government and authorities has improved over time and today there is a much more open dialogue to define how to make innovation available at public institutions," points out Ugo de Jacobis, president and general director of AstraZeneca. Alexis Serlin, country president of Novartis Mexico, confirms that "drug access is high on the agenda. Thus, we are partnering with the Ministry of Health to make sure innovation gets to patients in an economically efficient way for the government." Peña at GSK shares the same view: "From an industry perspective we have been trying to understand the difficulties the government is facing and opening a dialogue to find mechanisms to fix pricing to work together and make drug access possible," and adds that "it is important to create the dialogue and make it happen."

NAVIGATING THE NEW RETAIL ARENA

Two important trends are shaping the pharmaceutical retail scenario, forcing local as well as international companies alike to rethink their go-to-market strategies. First, a reconfiguration of the retail segment with the consolidation of pharmacy and supermarket chains and the market entry of new players; and second, the presence of physicians at points of sale.

According to IMS Health, chains and supermarkets went from holding 45 percent market share in 2008 to 59 percent in 2013. By mid of 2014 three pharmacy chains – Benavides, Farmacias Guadalajara and Farmacias del Ahorro – controlled almost 90 percent of pharmacies in the country and are increasingly becoming a preferred option for customers. The recent announcement of drug store retailer Alliance Boots' acquisition of Farmacias Benavides as well as the market entry of non-pharmaceutical retail players such as Femsa, owner of Mexico's leading convenience store chain Oxxo, indicates the segment offers interesting growth perspectives and may bring in new business practices.

The apparently incessant growth of big pharma chains may also force wholesalers to reinvent themselves, especially after the collapse of one of the historic players, Casa Saba, which declared bankruptcy at the beginning of 2014. "We have shifted from a distribution model with a small number of large wholesalers to a system with a small number of large pharmacy chains," points out Americo García, general director for Northern Latin America at Apotex.

However, the real big game changer in the industry are physicians at the point of sale. Karel J. Fucikovsky, general director for Mexico and Central America at the French drug maker Pierre Fabre, thinks "the emerging power of physicians at the different points of purchase and pharmacies is a trend pretty unique to Mexico and the Latin American region and growing incredibly at the moment." And the numbers confirm Fucikovsky's belief.

From left: Karel J. Fucikovsky, general director for Mexico and Central America at Pierre Fabre; Ugo de Jacobis, president and general director AstraZeneca

According to COFEPRIS, out of the nearly 28,000 pharmacies that exist in Mexico today 54 percent offer medical consultation, 340 percent more than in 2010. Also, IMS Health estimates that pharmacies provide over 250,000 medical visits on a daily basis – an impressive number considering IMSS provides nearly 290,000. "This has been a phenomenon that no one in the past has been taking into account very seriously, but that will eventually make pharmaceutical companies refocus their strategies to understand this dynamic and emerging market, as to better work with it rather than against it," concludes Fucikovsky.

Opinions on the presence of physicians at the point of sale are split within the industry. On the one hand, many think it represents unfair competition, as doctors tend to prescribe store brands. In today's retail scenario "the point of sale plays an increasingly important role in the business equa-

tion," points out Carlos Abelleyra, CEO for Spanish Latin America at Aspen. "The prescription switching pharmacy chains are doing from branded generics to private labels is huge and it is challenging to assess, as it is not audited. And this is jeopardizing the price strategy companies have at normal pharmacy chains." Rafael Gual from CANIFARMA warns against the practice as well. "The trend is here to stay, it is a necessary evil. We must remember a medical consultation at a point of sale is far from being equivalent to one at a medical institution." On the other hand, many think it can help diminish the chronic habit of Mexicans towards self-medication, while it unburdens the public healthcare system and fosters prevention.

And more changes can be expected in the turbulent medicine retail arena. José Alarcón Irigoyen, partner and leader of the Healthcare Practice for Mexico and Hispanic America at PwC, thinks the industry can even expect more disruptive approaches: "The innovation may come from looking at alliances with hospital chains and retail chains with point-of-sale physicians to act together as a new player and offer an integrated healthcare delivery network, whereby the physician at the pharmacy will reference the patient requiring further attention to a clinic of this network through a financial model based on micro-insurances complemented with a model to manage the health of such citizens in an integrated way." Only time will tell.

BIGGER FOOTPRINTS

Besides a stable business environment and optimistic outlook, Mexico offers companies in the pharmaceutical arena an additional advantage: manufacturing cost competitiveness. According to the 2014 BCG Global Manufacturing Cost Competitiveness Index, average direct manufacturing costs in Mexico are 4 percentage points cheaper than China's, with the country's overall cost structure presenting the best improvement among the 25 economies in the index. The same is true for the pharmaceutical industry. According to KPMG's 2014 Competitive Alternatives report, in 2014 Mexico's manufacturing costs for the pharmaceutical industry were 14.4 percent cheaper than the US.

For this reason an increasing number of companies in recent years have announced significant investments to strengthen their local footprint in the country. In the effort to ramp up manufacturing operations to meet increasing international demand, Takeda has chosen Mexico for its cost competitiveness and is currently upgrading its local infrastructure. "The Takeda Mexico plant started operations in 1961 and has had two large reno-

vations since then. Today, it exports to 16 countries including Colombia, Argentina, Peru, Ecuador and Venezuela. It has certifications from COFEPRIS, Safe Company from the Ministry of Labor, Clean Industry from the Federal Attorney for Environmental Protection (PROFEPA) and INVIMA from Colombia, in addition to several, continuous audits," explains José Manuel Caamaño, general manager of the Mexican affiliate. "For the past nine months, our plant was completely refurbished to become a best-in-class plant with top technology and high-quality staff." The local footprint has also helped the company have the flexibility to better adapt to the local needs of the market. "We have developed a product portfolio specifically tailored to the country: The four areas we will be focusing on locally are primary care and high specialty, with treatments in the therapeutic areas cardio-metabolic, oncology and gastrointestinal. Takeda Mexico has successfully launched eleven products in three years in Mexico. We are definitely committed to bringing innovative products for a better health of our patients."

Yet, advantages go well beyond cost competitiveness. "We compete not only with regional, but also with international production sites at a global level. The level of productivity we can achieve in this type of environment is high thanks to the lower cost of manufacturing, but also due to the level of human capital

From left: Carlos Abelleyra Cordero, CEO for Spanish Latin America at Aspen; José Manuel Caamaño, general manager of Takeda; Juan José Davidovich, general manager of Sifi Group

available – Mexico offers the right mix," points out Pedro Galvís at Merck, which in 2013 announced an investment of USD 10 million to increase the manufacturing capacity of the local subsidiary. "Having manufacturing located here in Mexico gives us flexibility and it pays off – we have one of the most competitive manufacturing costs worldwide."

Aspen is also betting on Mexico. The South African giant is decided to transform Latin America into the third pillar of success for the group, after its origin country and Australia – and has decided to leverage local production in Mexico to do so. To make this happen Aspen appointed Carlos Abelleyra Cordero, with more than 20 years of experience in the industry, CEO

New (Indian) kids on the block

Foreign companies are increasingly interested in tapping into the luring Mexican and Latin American pharmaceutical markets, and Indian companies are no exception. "Glenmark entering Mexico was part of a greater corporate global strategy," explains Eugenio García Verde, country manager of the Mexico affiliate. "Having established the brand in key markets across Asia, Africa, Europe and the United States, Glenmark started its expansion towards emerging countries [in Latin America]." The reasons for API and drug manufacturer Hetero were similar, explains the general manager Adrián Ruíz: "The company chose the country mainly because of the great work done by Mikel Arriola at COFEPRIS to create a solid regulatory environment for the pharmaceutical industry." Today, "Mexico represents a strategic hub to access and control further operations in Latin America."

The market entry, though, is not free of hindrances. "One of our biggest challenges has been the inaccurate perception associated to the low quality of Indian products," comments García Verde. "Fortunately, this is changing. The way we are overcoming this perception is through the development of stronger brand equity with high quality products commercialized as branded generics and innovative products." On the other hand, Ruíz stresses the difficulties of making the local market understand the advantages of more expensive products in the API segment: "competition from Asian manufacturers is fierce. Hetero is a company that complies with all best manufacturing practices required by the industry, so does not offer a cheap product. Yet, we offer advantages in the mid- to long-term, as due to the high quality of ingredients, the quality assurance process is more effective, registration is faster and documentation more transparent."

Eugenio García Verde, country manager of Glenmark

Adrián Ruíz, general manager of Hetero

Despite the difficulties, both companies have bold plans for their respective local affiliates, leveraging unattended market niches and a 100 percent Mexican management. "Glenmark does not always operate strictly in the same therapeutic areas across the world. In Mexico, for example, we decided to focus on dermatology because of timing and opportunity," explains García Verde. And the focus is bringing results: in four years the company has launched more than 20 prescription drugs, moving into additional therapeutic areas where the company wants to grow, such as respiratory and oncology.

Hetero's plans do not lag behind either. As of today the company relies on 12 business-to-business API contracts, nearly 50 products negotiated and agreed, 22 registrations and eight production plants in India already inspected and approved by COFEPRIS. "Moreover, we have established three joint ventures with Mexican companies to have local manufacturing with the possibility of acquiring them in the mid- to long-term" adds Ruíz enthusiastically. Time for the new Indian kids on the block to be bold.

10 Leading corporations by value in the total market (*)		
1	PFIZER CORP.	6.4
2	SANOFI CORP	5.7
3	BAYER CORP.	5.4
4	NOVARTIS CORP.	4.6
5	SCHERING PLOUGH C	4.4
6	BOEHRINGER ING.CO	3.8
7	SANFER CORP.	3.2
8	MERCK-SERONO	3.1
9	JOHNSON JOHNSON CO	3.0
10	SENOSIAIN	3.0
		42.41

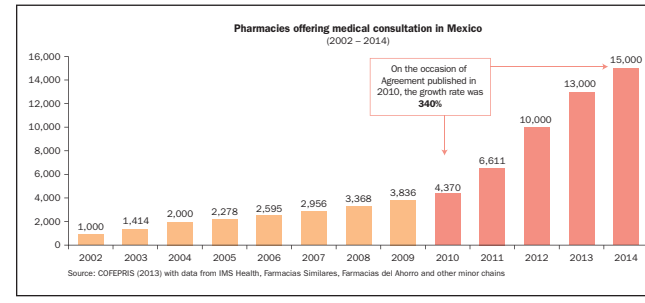
(*August 2014) Courtesy of IMS Health

for Spanish Latin America. Former general director for Wyeth Mexico and Central America, today Abelleyra is charged with the mission of successfully integrating the infant nutrition business Aspen acquired from Nestlé back in 2013. "When I was appointed CEO I knew the goal was to lay the foundations to create Aspen Latin America – and that's what we are doing." Part of the deal included the acquisition of a production facility in Mexico the South African drug maker plans to use to penetrate the region. "We plan to invest USD 20 million to dou-

ble the current production capacities. In the mid- to long-term the idea is to have a full pharmaceutical production plant based here, which can be a hub for the region." What stands out about the adventure of Aspen in Latin America is that the company is going a different way. "Aspen used to be a 100 percent generics company, and in South Africa and Australia it still is. But in Latin America the generics space faces fierce competition from local manufacturers and prescription still represents an important purchasing driver, so we decided to adapt to the local scenario and change the strategy from a basket to a therapeutic area company." And the long-term objectives are ambitious, as Abelleyra plans to achieve USD 1 billion regional sales by 2020.

Rafael Suarez, country manager Ferring

Also the Swiss specialty biopharmaceutical group Ferring is going the same way. "The company has a very clear idea about where they want to be – globally, regionally and locally," explains Rafael Suarez, country manager of the Mexican affiliate. "To strengthen its commitment to Mexico – the second market in the region after Brazil – back in 2008 Ferring bought a manufacturing facility in the State of Mexico, where we repackage imported bulk products for the local market as well as for Ferring subsidiaries in Central and South America."



Boehringer Ingelheim, which is turning 130 in 2015, has also announced the intention to scale up local operations. "Since 1995 Mexico has been appointed a strategic production site by the corporate," explains Salazar, who in May 2014 announced the company's plan to invest nearly USD 26 million to increase production capacities in Mexico. "We are also planning to convert Mexico in a hub for the manufacturing of diabetes products to then distribute them to the whole world."

Besides cost competitiveness, also other factors have encouraged companies to strengthen their foothold in the country. Mexico today is one of the most open economies in the world

with 45 free trade agreements in place and currently negotiating the Trans-Pacific Partnership (TPP) with other eleven countries of the Asia-Pacific region. It is the case of the Italian ophthalmology leader Sifi Group. "We looked at countries such as Chile, Brazil and Peru as a new base to enter the Americas, taking into account market dimensions, language barriers, cultural differences and facilities," explains Juan José Davidovich, general manager of the local affiliate. "We soon identified an ease of business in Mexico and decided to look for a partner here." And the ambitions for the group in Mexico are high. "The role that Mexico will play for Sifi, will be that of a hub to enter Central and South America," explains Davidovich. "This because of Mexico's agreements with other Latin American countries such as Chile and Colombia, which will greatly facilitate our operations in the region."

From left: Raúl Vivar, head of Shire Mexico, Central America and Caribbean; Elvin Penn, general manager of Amgen

RARE IS THE NEW FOCUS

According to the Mexican Organization for Rare Diseases, seven million Mexicans suffer from a rare condition, defined as one that affects less than five in 10,000 of the general population. "Physicians do not normally have these types of diseases in mind and their procedures and testing are not always adequate," explains Raúl Vivar, head of Shire Mexico, Central America and Caribbean. The challenges related to diagnosis are even higher when it comes to ultra-rare diseases, as it is the case of paroxysmal nocturnal hemoglobinuria (PNH), a condition in which red blood cells break down earlier than normal. "In case of rare diseases we are talking about five in 10,000 people. But in case of ultra-rare diseases it's five in a million," points out Luis Calderón, general manager of Alexion in Mexico" Early recognition of ultra-rare diseases is still a

Alexion: ramping up for the future

Luis Calderón, general manager of Alexion

The story behind Soliris goes back to 1992. The monoclonal antibody drug, which had been originally tested to treat rheumatoid arthritis and kidney diseases, turned out to be the first and only effective treatment for patients with paroxysymal nocturnal hemoglobinuria (PNH), an ultra-rare disorder that causes destruction of red blood cells. Since then, the drug has also been approved for a further rare condition, atypical hemolytic uremic syndrome (aHUS), which affects kidney function.

In Mexico the adventure of Alexion, the drug maker marketing Soliris, started in 2011, with the first sale coming one year later. "Today we distribute the drug only for PNH," explains Luis Calderón, general manager of Alexion in Mexico, "but we are ramping up for the launch of three new indications coming out within the next three to four years."

As it is the case for any rare disease, early and correct diagnosis is the name of the game. Physicians are "so focused on other pathologies that they may easily miss these, and by the time they are diagnosed it might already be too late," explains Calderón. For this reason Alexion is actively involved in helping patients and the medical community bridge the gap. "We are collaborating with several medical institutions in Mexico, such as the Mexican Hematology Association, which has a special group of approximately 20 physicians focusing on PNH."

And the efforts are paying off: over the past four years the company has reached triple-digit growth rate in Mexico and is preparing the launch of new indications. When asked about how it is to come from traditional drug makers and now work for an ultra-specialized company, Calderón points out that "whereas previously in an educational program with physicians you would probably spend only up to 30 percent of time discussing patients' cases, now you spend 90 percent of the time discussing them," as each patient and case is unique.

challenge. The probability for a physician to meet such a patient is very low. It's something, which is not their everyday, so we need to make them think out of the box."

Access to treatment is also a hurdle patients face in Mexico, as it depends on the healthcare provider they are affiliated with. "Fortunately our products for lysosomal diseases are all available at the different public institutions. However, the situation is different at every healthcare provider," explains Vivar. The public insurance scheme Seguro Popular, due to budget constraints, only covers patients who start treatment before the age of ten and only at a very limited number of certified hospitals across the country, which in turn imply a burden of costs for patients and their families. At the Mexican Institute for Social Security (IMSS), on the other hand, the main hindrance is the time between diagnosis and beginning of the treatment, which can span up to 18 months –too long for such a life-threatening condition.

Good news is that in recent years Mexican health authorities have shown an increasing openness towards recognizing the importance of correctly diagnose and treat rare diseases. The first step was a change implemented to Article 224 of the Health Law in 2012, which officially acknowledged the existence of orphan drugs, and thus rare diseases. The regulatory authority COFEPRIS has also shown an increasing concern with the treatment of rare diseases and since 2012 has granted market access to 19 new orphan drugs. This renewed openness has attracted new international orphan drug companies, such as Celgene, Eisai and BioMarin, to enter the Mexican market and to bring together stakeholders to make sure these conditions receive the correct recognition. "A problem of this magnitude has not an easy solution and should be addressed by different stakeholders, such as physicians, patient organizations, education institutions, public healthcare providers," adds Vivar. "To make sure we can raise the necessary awareness we are starting collaborations with different parties such as the Mexican Association of Pharmaceutical Research Industries (AMIIF) and other drug companies focusing on rare diseases."

With the recent opening of IMSS to clinical research, the Mexican market is also very interesting in terms of R&D in this field. Amgen envisioned this almost a decade ago, when the company decided to establish its first affiliate in Latin America in Mexico. "What started back in 2006 as an R&D hub intended to cover the rest of Latin America has received over the last eight years an investment of over USD 22 million in clinical research," explains Elvin Penn, new executive director and general manager at the Mexican affiliate. Today the company has 21 clinical trials running at leading research institutions in Mexico and plans to keep generating clinical data in the country for local as well as global registration processes.

A New CellTx Index?

The second half of March gave us two revealing captions for our updated sketch of the CAR-T space, which has already provided enticing early clinical results and staggering investor intrigue. Treatments using the chimeric antigen receptor-engineered T cells (CAR-T) have impressed so far, targeting various cancers including acute lymphoblastic leukemia, chronic lymphocytic leukemia, B-cell lymphoma, and others. First, Juno released its yearly 10-K to raised eyebrows. An $182 million R&D spend in the fourth quarter of last year caused a collective double take from the investment community. Then, after brushing off Juno's reveal, and in a display of defiance to "bubble" grumblings, rival Cellectis coolly pulled in $228 million in its initial public offering.

Confidence is high for CAR-T, and the sentiment spans to other cell therapies and gene editing tools for oncology and regenerative medicine. The sense that these technologies are just beginning to hit their stride has researchers and investors comparing themselves to the trendsetters of the early biologics era—with perhaps an even greater level of exuberance given the potential of real cures.

If you're one who tracks indexes, and thinks of companies in bins like large cap, mid cap, small cap and draws the distinction—biotech vs. pharma, you have cell therapy companies classified as biotechs, with expanding caps, no doubt. Granted, they are developing biological therapies, but delivering cells is a whole new beast from delivering monoclonal antibodies.

How different are these companies? How revolutionary is this space? How much do manufacturing, logistics, corporate culture, etc. vary from biotech? And of course, if we really do see cures, how different will pricing and revenues look?

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Today, the biotech vs. pharma fence remains somewhat divisive. For some companies, the terms paint a historical context, but sensibly, biotech vs. pharma is largely in name only. Big Pharmas have biologic therapies. Biotechs develop small molecules.

When biotechs hit the runway, they were drastically different from traditional pharmaceuticals. Biotechs invoked a West Coast, shorts and sandals attitude in contrast to the East Coast starched collars of pharma. Companies were smaller, the science was bigger, manufacturing was a new breed, and investing was volatile. But more importantly, their drugs were huge, both the molecules and the markets, with astounding results for patients, and price tags to match.

So far, I've yet to see any distinct cultural difference with cell therapy companies—let me know if any stereotypes do exist. But do the string of massive IPOs, and Juno's enormous 4Q receipt start to paint a picture of a space with drastic strategic differences from traditional pharmas and biotechs?

First, the technology is different. Though remaining in the realm of biological systems, culturing, treating, and delivering cells, either autologous or allogeneic, is entirely different from biotech treatments. Companies developing cells as therapies are challenged by issues like quality and assurance at entirely new levels. "Know your cells" is something said at cell therapy conferences, especially when a company has to undertake scaling up from treating perhaps dozens of patients in Phase I trials, to hundreds and more. Additionally, cell therapy makers talk of cell counts and thresholds rather than dose and toxicity levels.

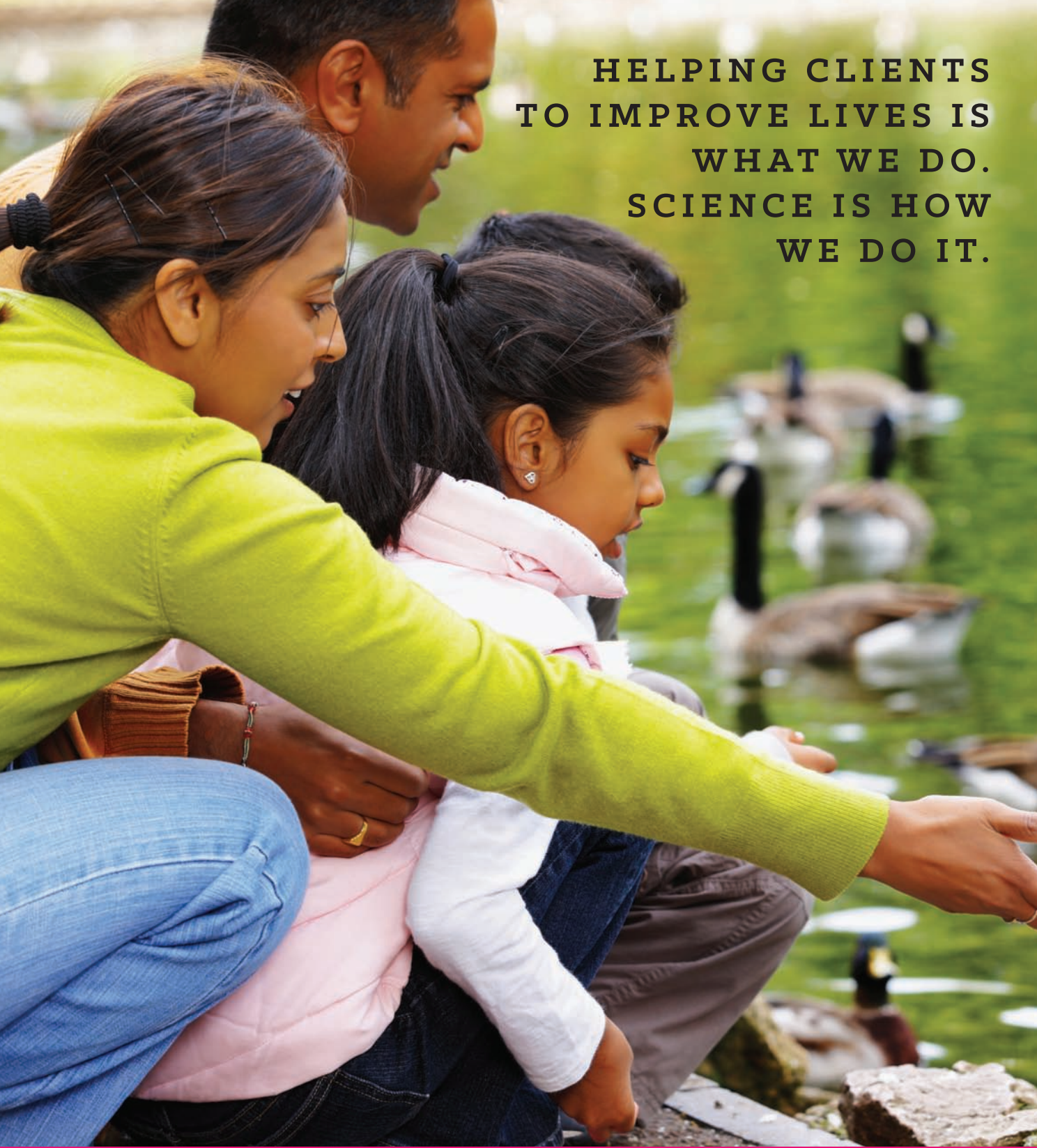
Second, many cell therapies will require a whole new level of logistics for delivering treatments to patients around the world. Extracting tissue from a patient, sending it to a lab for treatment, and delivering it back to the correct patient, all with cold chain storage, generates myriad levels of complexity when scaling up for large patient populations.

With some of these factors in mind, it's not difficult to imagine why some startup or buildup costs could be much bigger than anything Amgen or Genentech had to deal with early on. $182 million spent in three months won't be the norm for Juno every quarter, but other cell therapy companies will likely rack up big bills.

Due to early stage costs, there's a push for cell therapies and regenerative medicines developers to receive certain regulatory graces. If Japan's experiment with offering early conditional marketing approval based on safety and some minimal evidence of efficacy is productive, cell therapy firms could operate under different regulatory conditions than pharma and biotech in other nations.

Finally, as cell therapy and gene editing developers really start to use the "c" word—cure—pricing experts and payers will have to rethink the model that served pharma and withstood the biotech revolution. Will this change the way cure manufacturers will approach revenue? Will blockbusters be judged, not by their yearly status as billion-dollar blockbusters, but their 10 or 20-year status for multibillion dollars via annuities?

So we ask, (as a magazine whose very title pays homage to the suit and tie world of pharma), do we need to look at cell therapy companies differently—even distinct from biotech? Are cell therapies, gene editing, and regenerative medicines emblematic of a revolutionary period on par or greater than what biotech signified to pharma? Do companies offering cells or gene editing therapies rather than antibodies come with different enough profiles to ride their own NASDAQ indices? Or better yet, do companies who can bring real cures deserve their own stock exchange grouping? PE



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