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Twisting the Spigot

THIS MONTH, PHARM EXEC TAKES ITS ANNUAL LOOK at the state of the industry’s new drug pipeline. Not only is there much to please the expectant eye of Wall Street, there is more evidence to show that drugmakers commercial interests are better aligned with unmet medical need. “Me-too” drugs designed to grab that extra helping of profits with no heavy lifting on the clinical side are now the exception, not the rule.

The latest FDA statistics on the 29 novel drug approvals so far this year provide the proof point. Fifteen of the 29 secured status under the FDA's four review categories covering the best, most advanced science—Accelerated, Breakthrough, Priority, and Fast Track—while seven drugs won separate listing as orphan drugs for patients with rare, usually untreatable diseases. One drug, Apyraz, from Actavis, was also selected as a Qualified Infectious Disease Product (QIDP), the fifth industry-developed medicine approved to address the absence of therapies for drug-resistant, life-threatening bacterial infections.

Building on Senior Editor Casey McDonald’s timely synthesis of 2016’s best new fields and targets, I see four key themes driving the fast-changing environment for drug development.

The first is complexity. This is due to convergence between great science; the interpretive power of information processing technologies; and rising clinician and patient expectations. R&D priorities, once focused on the open-ended metric of delivering the biggest number of “shots on goal,” now rest on a precise commitment to quality, not volume. There is significantly more risk, not to mention expense, in applying advanced tools of molecular biology to find the right target in the right patient population and to ensure the target is translatable to a human disease. This, in turn, requires data and evidence, relevant to that disease state, to prove the target can fulfill its potential as a clinically differentiated, reimbursable medicine that appeals to payers.

Most important, all this must be done very early in the commercialization cycle, so far forward that the original depiction of disease states may be altered beyond recognition by competitor successes or progress in the underlying science. All told, the basic activities of new drug development have morphed from simply proving, on the basis of narrowly hypothesized criteria, why a compound should be licensed to justifying, to a much larger group of stakeholders, why that compound should actually be prescribed.

This leads to our second theme, which is diversity. This can be measured in many ways, beginning with the sheer proliferation of research collaborations, which are now common among big Pharma firms that just a decade ago shunned them on competitive grounds. R&D is also being shaped by the erosion of the traditional separation between the pharmaceuticals, biotech, and generic sides of the business. Binding all is a competitive push to innovate, even in generics, where process, quality, and supply chain excellence are critical to counter increased pressure on margins. For biotech and pharma, convergence has made the search for talent more mobile and competitive, especially as smaller start-ups find it easier to staff up with exiles from the biggest R&D players.

And there is the direct engagement of non-profit professional and patient organizations in drug development, exemplified by the Cystic Fibrosis Foundation’s pioneering venture philanthropy model: a modest $150 million stake it took back in 2000 on a promising Vertex drug candidate, Kalydeco, paid off handsomely last year when it sold its royalty rights for $3.3 billion, instantly giving it a research budget equivalent to any mid-sized pharma.

While there is a solid rationale for this and other public-private partnerships, especially at the pre-competitive stage, questions remain on whether the proliferation of deals might be causing duplication that is wasteful of R&D investment and the efficient deployment of scarce human resources. We may see pressure for more international agreement before proceeding with individual programs.

The third theme is transparency, evidenced by the continuing efforts of government, academia, and NGOs to promote “open innovation” models, dismantle IP standards, and regulate disclosure of trial results. Post-marketing study requirements—now estimated to comprise a fifth or more of overall drug-development costs—are being driven as well by the push to shed light on real-world safety, side-effects, and the overall “value” of medicines in the clinical setting.

We end with viability. While it is premature to declare the death of big Pharma’s R&D mojo, suggestions abound about ways to do it better. We can start with the low-cost “frugal innovation” embodied by China and India. Adjacent businesses like Google and Apple may never actually develop or deliver drugs, but they have a far stronger hand in leveraging big data around a preventive, consumer-friendly health and wellness agenda. This strategy poses an alternative to the disease-centric “treat and cure” model of big industry R&D organizations.

Measuring against these four themes is one way to chart the future course of this ever-challenging ecosystem of R&D. Prepare to be disrupted.
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• What is real integrated multichannel engagement and what are the different areas covered under the term?
• What are the shifts that need to happen to bring integrated multichannel engagement to life?
• How to use analytics as part of your wider multichannel strategy.
Pharm Exec’s 2016 Pipeline Report
Casey McDonald, Senior Editor
Falling enterprise values and the drug pricing controversy have defined the life sciences landscape during the waning days of 2015. Will a pipeline harvest full of treatments founded on strong science, supportive regulation, and unmet medical need offer solace to shareholders and the promise of a reputational rebound?

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Supply Chain
Pharma’s ‘Push-to-Pull’ Mandate
Julian Upton, European & Online Editor
If biopharma doesn’t evolve its supply chain function in step with new technologies and new regulations, the industry could soon face unprecedented distribution and logistics challenges, experts warn. Pharm Exec explores ways companies can re-engineer their supply chain while there’s still time.

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Commercial Strategy
The Market Mix for Companion Dx
By Jeff Liepman, Kevin Barnett, Kun Lee, and Nathan Lyman
Amid the spate of targeted drug approvals in recent years and more biomarker-driven treatments on the horizon, marketing a therapy paired with a companion diagnostic can be a competitive plus. Four “can’t miss” strategies in managing the development, launch, and commercialization of Rx-Cdx pairings are outlined.

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Readers Weigh In

The most troubling and frankly disappointing point is that PhRMA and Rx leaders are actually still espousing the discredited illusion that the American public is not supportive of price controls. The public is indeed enraged. Physicians from top institutions are writing op-ed pieces on the cost of oncology drugs, publicly slamming pharma companies that are well deserving of the criticism. Other physicians are developing their own drug value models for their institutions and publishing them.

Jim Harmon, 10/19/15
“Hillary’s History on Rx Price Controls”
bit.ly/1PO1sRr

Twitter Talk

Must be judicious about data we collect—how data is used to benefit patient and investigator.

PM Clinical, @PMClinical, 10/8/15
“Relationship-Centric Technology: Improving the Human Experience for Better Engagement”
bit.ly/1KMbikK

UK consumers interested in #Healthcare wearables but still cautious over their #data.

IMS Health UK, @IMSGlobalUK, 10/7/15
“UK Consumers Cautious Over Healthcare Wearables”
bit.ly/1MfiOcl

Focus: Emerging Markets

Pharm Exec convenes a roundtable discussion to highlight current issues facing the biopharmaceutical industry in emerging markets.
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Trust our chain reaction
M&A Spurs Manufacturers’ Reliance on External Packaging Providers

M&As provide pharma companies with the opportunity to streamline operations and divest non-core competencies. Packaging and dispensing systems, due to increasing requirements related to consumer safety, product performance, supply security and environmental regulations, is prompting manufacturers to rely on the expertise and efficiencies of external packaging providers.

Change is the only constant in today’s biopharmaceutical industry as companies continue a frenzy of M&A activity to bolster business in a highly competitive landscape marked by patent expirations, dwindling pipelines and escalating costs pressures that face a new healthcare system.

For the first half of 2015, the total value in pharmaceutical M&A topped $221 billion, beating the $162 billion total for the whole of 2014 and averaging more than one life sciences acquisition per day, according to Laura Vitez at intelligence firm Thomson Reuters.1

And Vitez says the trend shows no signs of abating as companies begin adopting M&A as a strategic path to the future. Meanwhile, balance sheets are healthy. Pharmaceutical companies are still flush with cash. And the newly formed companies stand to benefit from a growing market with industry sales projected to grow almost 7% annually into 2018.2

**Leveraging packaging advantage**

M&A transactions provide opportunities for companies to scale back on redundant resources—plants, people and equipment become part of excess capacity in the integrated company’s manufacturing network. Many companies are also using deals as opportunities to streamline their operations—restructure and rescale while transferring non-core activities and costs to external partners.

Packaging and dispensing systems, in particular with increasing requirements related to consumer safety, product performance, supply security and environmental regulations, as well as the demand for sophisticated new packaging for specialized therapies (pharma’s fastest growing market) is prompting manufacturers to rely on the expertise and efficiencies of external packaging providers. In turn, these companies have become a driving force of the pharmaceutical packaging market (expected to grow at a CAGR of 8.38% to reach $86.7 billion by the end of 2019 from $57.9 billion).

Not so long ago packaging was viewed as having a single function only. Today, as Steven E. Kuehn, writes in a recent article of *Pharmaceutical Manufacturing*, packaging not only matters, it is quickly becoming one of the most important considerations in the growth and success of any drug product. Manufacturers now consider packaging key to the supply chain as well as essential to increasing sales by product differentiation in a competitive marketplace.

“It’s hard to understated the critical role pharmaceutical packaging plays in ensuring the efficient distribution and eventually, the safe consumption of the world’s drug supply,” says Kuehn, Editor in Chief of *Pharmaceutical Manufacturing* in his August/September issue. “And in 2015, it was asked to deliver even more to meet Pharma’s ever-expanding demand for packaging solutions to support the medical success of a given compound.”

**Time to switch**

Packaging’s benefit to a manufacturer’s top line includes improved adherence. The annual cost of non-adherence in...
the US is estimated to be $317 billion and $125 billion in the EU. Medication packaging has proven to be a uniquely effective adherence intervention, giving people the tools they need to change their adherence behavior, including reminder cues, disease and treatment education, and consistent reinforcement.

The right packaging is also essential in dispensing those therapies (most often injectables) that target rare diseases or previously untreated diseases and/or specific therapeutic areas, such as cancer and neurodegenerative diseases. These specialty pharmaceuticals often require extended courses of treatments and innovative packaging to improve delivery, adherence and outcomes.

The resource reductions inherent in M&A deals make cost efficiencies when outsourcing packaging a priority to the manufacturer at the newly acquiring companies. Similarly, the multifaceted importance of packaging in the development and commercialization of a drug underscores the necessity of a full-service provider who can deliver both cost-effective solutions and also strategies for growth.

Cost effective

“The right packaging provider can add significant value for the company and impact the bottom line in package or filling cost savings, supply security, reduced lead times/inventory reduction, better service offerings, as well as to the top line by improving adherence or satisfaction, which drive refills and loyalty,” says Stacy Buchanan, Strategic Marketing Director, Healthcare Dispensing Systems, at WestRock, a global consumer and corrugated packaging and dispensing systems company.

“Whatever your business objectives – from launching a new product to creating a line extension to simply seeking an alternative supplier – the right packaging provider can help fill the gaps to pave the way for growth.”

WestRock, a $16 Billion company with 40,000 employees, is itself newly formed from a merger finalized on July 1, 2015, between Rock-Tenn Company (RockTenn) and MeadWestvaco Corporation (MWV), two large packaging companies.

“Our global presence, and sheer size and strength, reduces risk for customers,” says Buchanan. “We are financially strong. We can make investments in things like capacity and insights research. We have expertise and excellent quality standards. The combination of deep industry experience, a dedicated team of experts and an organizational commitment to serving the pharmaceutical market allows us to be nimble and responsive, more like a small organization would be.

“Say, for instance, a customer is changing packaging format or even packaging suppliers, it may mean changes on the filling line. And so, we have machinery experts and technical teams that can work with customers to help make any modification to their existing equipment and provide support during validation.”

The switching process need not be a burdensome or costly if the right provider is brought on. “Real value doesn’t come from a supplier. It comes from a partner,” says Buchanan. “A partner can bring in experts in various functional areas, whether it’s regulatory or lab or supply chain or manufacturing – all the different functional areas – that can either fill your resource gaps from a service perspective or connect you with the other right partners like fillers or contract manufacturers and machinery suppliers. And from a broader perspective, WestRock is a company formed from two of the largest global packaging industry leaders.

We have all of those collective resources and strength that companies can rely on.

“And when it comes to developing innovative packaging, we have the experience and understanding that the best designs emerge from the best insights. We stay abreast of the trends. We appreciate what makes the pharmaceutical market special and importantly, we engage deeply to understand the customer. When packaging integrates patients’ needs and preferences into the design, the packaging serves more of a purpose than just containing medication or meeting a regulation. In the case of CR design, for example, what developments is packaging that keeps children safer, improves ease-of-use for adults, and provides a positive patient experience.”

In turn, explains Buchanan, innovative, patient-centric packaging can function well beyond regulations to fulfill patient needs and preferences.

“Insight into our customers’ preferences enables a better user experience, enhanced adherence, the potential for improved outcomes, and increased sales,” says Buchanan. “So, yes, what is needed is a packaging provider who can partner with you to not only facilitate the change process and fill resource gaps, but also help drive your company’s growth in this mega merger world we’re all operating in.”

References
Drug-Pricing Backlash Reaches Fever Pitch

Doctors, advocates, politicians, and the Feds jump on price-gouging bandwagon

Another day, another attack on exorbitant drug prices. Cancer centers pay more attention to cost in selecting treatment options. Plans and pharmacy benefit managers (PBMs) impose strict limits on prescribing of hepatitis C virus (HCV) treatments and new anti-cholesterol drugs to control outlays. Turing Pharmaceutical’s 50-fold boost in the price of an old anti-infective treatment ignites moves to curtail drug spending on all fronts. Collateral damage may emerge in reduced support for legislation authorizing added incentives for biomedical innovation and for intellectual property protections around the world.

While most complaints have targeted costly new specialty drugs, activities by Turing and Valeant Pharmaceuticals have focused attention on hefty price hikes for old medicines, often following product or producer acquisition. Even generic drug makers are under scrutiny following steep increases for traditionally cheap, widely used parenterals.

Industry marketing practices, moreover, are driving investigations of whether Valeant has violated anti-kickback laws and policies governing patient assistance programs. And Turing has raised antitrust issues related to using a closed distribution system to prevent generic drug competition. Sen. Amy Klobuchar (D-MN) called for the Federal Trade Commission to probe this issue, while the New York attorney general launched an investigation. Generic drug firms have long complained that narrow distribution programs established under risk evaluation and mitigation strategies (REMS) make it difficult to obtain drug samples needed for bioequivalence testing.

Numerous polls show that consumers want the government to take action to curb drug costs, and the politicians are responding. Hillary Clinton rolled out a plan for lowering prescription drug spending in September that emphasizes evaluating medical products based on value and speeding more new generic drugs and biosimilars to market. Clinton wants to end “pay-for-delay” deals, permit drug imports from abroad, end tax deductions for DTC advertising, and require drugmakers to spend a specific portion of profits on R&D. The only good news for pharma is Clinton’s proposal that insurers limit beneficiary co-pays for drugs to make therapies more affordable for patients.

Managing Medicare

Clinton’s list also includes the perennial price control strategy of allowing Medicare to negotiate prices for drugs covered by Medicare Part D drug plans. Such proposals have gained traction as Medicare spending on pharmaceuticals has begun to climb after several years of flat growth. A huge (52%) increase in premiums for about 18 million Medicare Part B beneficiaries, which covers drugs provided by doctors and clinics, plus looming premium hikes for Part D plans, is prompting greater focus on how costly prescription drugs may drive these trends.

The Medicare Payment Advisory Commission (MedPAC) is conducting a broad discussion of Medicare drug coverage and payment policies. An important issue is whether greater use of more expensive specialty drugs will shift more beneficiaries into the Part D “catastrophic” program funded by the government. The Commission plans to make recommendations next year on a range of coverage strategies, including better drug utilization management, improved medication adherence, and programs for “bundling” payments for cancer care.

Calculating value

Medicare also is launching a value-based insurance design model in 2017, which allows certain Medicare Advantage plans to test whether reduced patient cost-sharing for services and prescription drugs can improve care and save money for beneficiaries with chronic conditions such as diabetes and heart disease. The initiative reflects widespread interest in assessing the value of pharmaceuticals and whether higher costs are justified by improved product efficacy or safety. Payers and plans say they will ante up for high-value therapies, and pharma companies are looking more seriously at pay-for-performance deals linked to reimbursement.

This is generating demand for independent, credible methods for...
calculating, say, the value of preventing a heart attack or of providing an additional year of life. Not surprising, there is considerable disagreement over how to assess drug benefits, risks and affordability, as seen in the ongoing discussion of the cost of new PCSK9 inhibitors (Amgen’s Repatha and Praluent from Sanofi and Regeneron) to control very high cholesterol.

A September report by the Institute for Clinical and Economic Review (ICER) criticized $14,000 list prices for these new therapies and concluded that $4000 better reflects their value. At a recent symposium sponsored by the Pew Charitable Trusts, Amgen senior vice president Josh Ofman charged that the ICER assessment focused too much on short-term affordability as opposed to long-term health benefits, and that ICER systematically under-estimates population risk and over-estimates the likely uptake of these drugs. ICER president Steven Pearson responded testily that he’s “very proud of our work” and that pharma companies can’t expect “a blank check anymore” to cover costly medicines.

The National Pharmaceutical Council (NPC) separately critiqued ICER’s value assessment framework, calling for greater transparency in its models, assumptions, and data used in evaluating treatments. NPC questions how ICER calculates drug uptake rates and emphasizes the need to recognize changes in treatment value over longer time periods.

A common pharma complaint is that analysts too often use drug list prices in calculating costs and benefits and ignore the discounts and rebates routinely negotiated by payers in their assessments. The ability of PBMs to obtain much lower prices from manufacturers was clear in Express Scripts’ announcement that it will cover both of the new anti-cholesterol drugs due to hefty company price concessions. Last year, Express Scripts and other PBMs used competitive bidding to select only one of the new HCV treatments for formulary placement, decisions that upset many consumers.

Express Scripts plans to manage the cost of the new cholesterol therapies with strict patient utilization and step-therapy strategies, noted senior vice president Steve Miller. And more sophisticated data systems that can help determine if a patient has previously used statins and the outcome will enable the plan to better target prescribing to individuals unable to control extremely high cholesterol levels, as per FDA-approved labeling.

Another day, another attack on exorbitant drug prices. … Collateral damage may emerge in reduced support for legislation authorizing added incentives for biomedical innovation and for IP protections around the world
Falling enterprise values have defined the life sciences landscape during these waning days of 2015, accompanied by a storm cloud of negative headlines on industry pricing practices. This, in turn, has fueled the ire of skeptical payers, politicians, and the public at large. Will a drug pipeline harvest full of treatments founded on strong science, supportive regulation, and unmet medical need offer solace to shareholders and the promise of a reputational rebound? Will presidential politics add to the pressures on drug pricing, with a sour coda to the old refrain, “in the US, the market decides?”

By Casey McDonald

Well before their fall leafer excursions to the deciduous tracts north of the Boston-Philadelphia life science corridor, investors were seeing red. But the harsh crimson taint adorning their company’s stock ticker isn’t bringing the same seasonal enjoyment as the red, orange, and yellow hues of the Maple, Beech, and Hickory.

Much as in nature, where trees that give up their foliage early are often afflicted by invasive pests, many in biopharma are looking to blame a 32-year-old, drug-hiking scrooge named Martin Shkreli and the pricing backlash he wrought. However, as the drug pricing controversy fails to clear and drugmakers and their investors continue to fear a punitive, politically motivated response, one wonders if the forest is simply seeing a correction trailing several years of growth, or if it represents the maturation of an unhealthy ecosystem primed for a more significant burn. In the latter view, that young CEO looks more like a kid playing with matches in a dry thicket.

Nevertheless, biopharma companies continue to reach for those patches of sunlight above the canopy,
counting on the potential in their pipelines and the massive markets with unmet medical needs waiting to be tapped. The argument against a bubble continues unchanged: that lofty valuations are justifiable given the stellar line of new products that have leapt into the market along with many others now salting through company pipelines. The successes of several recent launches have produced sales figures so impressive that those who had predicted “the end of the blockbuster era” not long ago, have quietly shelved their Carnac the Magnificent hats.

Helping the cause is a more accommodating regulatory process, to the point that some critics warn that the FDA might be too helpful to the industry. Both industry and the FDA assure critics that in comparison to the past years of friction, the evolving quality of basic science now means that drugs are coming forward with better safety and efficacy profiles. In addition, trials are better designed and better recruited. “FDA standards haven’t changed, but manufacturers are getting better at developing and supporting effective products through approvals,” noted Amy Grogg, senior vice president of strategy and commercialization, AmerisourceBergen Specialty Group.

The fact that many approvals have been for smaller indications geared to orphan disease populations means that drugs are better targeted to tighter patient populations. In orphan drugs subject to accelerated review for multiple myeloma, and an oral JAK inhibitor candidate targeting inhibition. more immediate gains in purely oncology may come from a trio of therapies now progressing into late-stage trials, and candidates from the bACe inhibitor group may follow.

But research continues that could produce fruit. A few long studied compounds are hanging on for dear life while new buds are sprouting. The market potential for anything, anything that could impact AD progression substantially would be tremendous, so even the slightest sign of progress creates excitement and thus major market interest and volatility.

For years, the industry has put its hope for a disease-modifying treatment in the amyloid hypothesis. The accumulation of plaques in the brain consisting of amyloid beta peptide has been investigated as the primary driver in the pathogenesis of the disease and the key target for a cure. The most advanced, and still with a reasonable chance of reaching the market, are two humanized monoclonal IgG1 antibodies targeting A-beta peptide, Eli Lilly’s solanezumab and Biogen’s aducanumab. The pair have been up and down, and are currently up, sort of, following trial data dumps at July’s Alzheimer’s Association International Conference in Washington, DC. Solanezumab had all but exited stage left after Phase III failures in 2012. But persistence could pay off for Lilly as it’s extended look study, Expedition-EXT, showed
The Patient Experience Project's innovative way of marketing brands for rare diseases offers pharma companies an opportunity to engage patients, caregivers, and healthcare professionals in a way that improves the lives of those living with rare diseases and, at the same time, drives business results.

Unique are pharmaceutical advertising executives who describe their marketing approach without mentioning KOLs, sales meetings, or other traditional marketing lingo. Instead, the PEP’s founders talk about patients and caregivers—finding them, meeting their needs, improving treatment experiences, and partnering with their communities to make a real impact. And, they do so with real empathy and passion for the potential to improve lives. Such was the interview Pharmaceutical Executive conducted with Patient Experience Project’s Founder and President Dan Bobear and Director of Patient Experience Strategy Kristin Phillips. Bobear and Phillips’ passion comes from a fundamental belief that the singular focus of pharma marketing should be to improve the patient experience.

Where Pharma Falls Short
“All of us at PEP came from professional marketing backgrounds—on the client side and on the agency side,” says Bobear. “We learned traditional pharma marketing developed during the blockbuster era that focused on marketing to large patient populations. Today, things have changed, and orphan products are being routinely developed for rare diseases. By their very nature, orphan drugs defy traditional pharma marketing approaches. Rare disease patient populations are small, making mass-market promotional approaches impractical and insensitive to the unique needs of each rare disease patient population. Patients are scattered geographically, isolated, and difficult to reach. Rare disease markets require a customized solution.”

The Need for a New Way
“We are at a turning point in this industry right now,” says Bobear. “The number of orphan disease brands and specialty brands coming to market is increasing dramatically. The fact is that rare diseases, when viewed collectively, aren’t that rare. Almost 30 million people in the United States, or one in 10 people, live with one of approximately 7,000 rare diseases. When you add in the expedited review and flexible FDA approval criteria for orphan disease products, this area has become very attractive to pharmaceutical manufacturers. This is especially true given the cost and difficulty of getting traditional products approved in more common therapeutic categories. According to a recent report, the global orphan drug market is expected to expand to $127 billion by 2018, as well as contributing 15.9 percent of the overall prescription drug market.

“We refer to rare disease brands as high-touch brands,” continued Bobear. “Rare disease patients and caregivers have more complex needs and demand much more than a pill. They need emotional support, connectivity to...
others like them, credible information about their condition, and available treatment options. To deliver on this need, marketers need to gain a real and authentic understanding of patients’ experiences with their condition and available treatments. It is critical to engage authentically with patients, caregivers, and the community because they know if they are being ‘sold’ to. They know if you are ‘for real.’ If you engage with these patient communities the right way, you will welcome you with open arms because they really need help; if approached the wrong way, they will shut you out.”

The PEP Approach

PEP has designed a structured approach for developing and marketing brands. “Our approach,” says Bobear, “spans the entire commercialization continuum from product development and healthcare professional marketing through targeted patient programs. All of these solutions are designed to enhance the brand experience by leveraging our deep understanding and insight into the patient experience as the core platform to engage and deliver brand value to both patients and their healthcare partners.”

“PEP is guided by three principles. First, content is king,” adds Bobear. “Patients with rare diseases, and their caregivers, crave communication that is authentic, dynamic, and engaging. Content also needs to be portable, meaning it can be shared easily online and via social media. Think about when people scan Facebook; they intuitively open up, engaging content that speaks to them, and they ignore the rest. PEP collaborates with rare disease patients, caregivers, and HCPs to develop what we call epic content that hits the mark and engages on a level that traditional pharma programs could only dream of before.

“We sit down with the families and co-create the content they need. They are the experts. They are the stars of the show and as a result, the content is highly connective and has an amazing impact.”

The agency’s second operating principal is that context is queen. “Where the content lives is just as important as what we say,” says Bobear. “PEP works directly with patient groups and partners with social communities. We use highly targeted media techniques to meet patients and caregivers where they are, as opposed to traditional media approaches that assume where patients will or ought to be. We target the placement of content and consider the way people will engage with it. Patients and caregivers share the content in their communities and everything takes off from there. In addition, it is important to create optimized content that the search engines will rank favorably. If you create great content, then it’s important that people can find it when they search. That’s where expertise in digital strategy and search pays huge dividends.

“Cookie cutter approaches won’t cut it if you just follow the third principal,” says Bobear. “Each rare disease is different, and PEP uses patient/caregiver workgroups and ethnographic research to understand the nuances of patients’ experiences—how they manage their condition, attitudes towards available treatments, interactions with their healthcare team, and family dynamics.”

Successful Returns

By adopting a patient experience framework, PEP challenges traditional thinking and creates unique and high-impact work. “It is created with disease experts, the patients and caregivers,” says Phillips. “Patients, caregivers, families, and marketers are drawn to The PEP approach. It adds deep meaning and enhances the work in an authentic and meaningful way. The approach is also having a positive effect on our clients’ business performance, which remains the acid test for company marketers. Healthcare is a business. Marketing medicines is a huge part. We are proud to play our part in transforming the lives of patients with rare diseases while contributing to the financial success of our clients.”
### Neurodegeneration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Phase</th>
<th>Catalyst</th>
<th>Estimated Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gantenerumab</td>
<td>Roche</td>
<td>III</td>
<td>2018</td>
<td>$7.6 billion by 2024</td>
</tr>
<tr>
<td>Adacanumab</td>
<td>Biogen</td>
<td>III</td>
<td>2018</td>
<td>$10 billion+</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Eli Lilly</td>
<td>III</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Ly3314814</td>
<td>Merck &amp; Co.</td>
<td>III</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>MK-8931</td>
<td>AstraZeneca</td>
<td>III</td>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>Cretinezumab</td>
<td>Roche-Genentech/AC Immune</td>
<td>III</td>
<td>2018</td>
<td></td>
</tr>
<tr>
<td>CNP520</td>
<td>Amgen/Novartis</td>
<td>I/IIa</td>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>RVT-101</td>
<td>Axovant</td>
<td>III</td>
<td>2018</td>
<td></td>
</tr>
<tr>
<td>Anavex 2-73</td>
<td>Anavex</td>
<td>III</td>
<td>2015</td>
<td></td>
</tr>
</tbody>
</table>

**Alzheimer’s Disease**

Drug Name: gantenerumab
- Company: Roche
- Phase: III
- Catalyst: Late 2016
- Estimated Sales: $7.6 billion by 2024

Drug Name: adacanumab
- Company: Biogen
- Phase: III
- Catalyst: 2018
- Estimated Sales: $10 billion+

Drug Name: solanezumab
- Company: Eli Lilly
- Phase: III
- Catalyst: Late 2016

Drug Name: ly3314814
- Company: Merck & Co.
- Phase: III
- Catalyst: Early 2015

Drug Name: MK-8931
- Company: AstraZeneca
- Phase: III
- Catalyst: 2017

Drug Name: crenezumab
- Company: Roche-Genentech/AC Immune
- Phase: III
- Catalyst: Late 2016

Drug Name: CNP520
- Company: Amgen/Novartis
- Phase: I/IIa
- Catalyst: 2017

Drug Name: RVT-101
- Company: Axovant
- Phase: III
- Catalyst: 2018

Drug Name: Anavex 2-73
- Company: Anavex
- Phase: II
- Catalyst: Nov 2015

An altered slope in the decline for patients who received the drug early, compared to those who first received placebo and then got the drug, a delayed start cohort. Not everyone is impressed, but for the optimistic, a slightly slower decline into AD ranks as a positive sign in a field that clearly needs one. Lilly’s 2,100-patient Phase III Expedition 3 trial should see its last patient visit in October 2016, a release date that puts it ahead of the competition.

Biogen’s aducanumab may benefit, or languish, from sharing the same target as solanezumab, depending on one’s level of optimism and what a second-place finish might mean. It also has recent data for which some are seeing the glass half-full; others are less excited. Optimists will point to the company’s positive results in a 166-patient Phase I trial released in March and the fact that the recent negative analysis could be about getting the right dose. Biogen is willing to wager on the pros and has started the five-year, Phase III program with 1,350 patients. Key data is expected in 2018 (Biogen reaffirmed its commitment to AD last month, announcing it was pruning its non-AD pipeline—and cutting 830 jobs in the process).

Roche also saw setbacks, but maintains its A-beta antibody program, gantenerumab, with Phase III trials active, and estimated completion dates listed in 2019 (Roche’s website lists filing as estimated in 2017). Roche/Genentech also announced its plans to progress the Phase III antibody, crenezumab, which is a humanized monoclonal antibody designed to target all forms of A-beta discovered by AC Immune.

Ultimately, for AD, population dynamics are on the drugmakers’ side. One widely held prediction estimates the proportion of the world’s population over 60 years of age doubling by 2050, from about 11% to 22%. The rising impact of AD on the healthcare system may hit the trillion-dollar mark, and a successful market launch of solanezumab could net Lilly $7.6 billion in yearly sales by 2024, according to a CNN Money report, citing an investment banker estimate. Of course, a discussion on value and analysis of the degree of benefit seen will go a long way to determine the price tag for any new AD treatment. Additionally, impacts in only patients with mild symptoms may limit the potential label of most value, while early diagnosis and a necessity to treat promptly at the first sign of AD may eventually see more patients on therapy.

With this massive market and the potential crisis for caring for so many dependent people in the healthcare system, the number of targets will continue to grow. But only time will tell whether AD treatments evolve as a step-therapy approach, or if the field takes a more aggressive trajectory with a combinatorial drug approach.

A subsequent batch of AD therapies could come from the BACE inhibitor group. Leading the class, Merck & Co.’s 1,960-patient, Phase II/III trial and a 1,500-patient Phase III trial for MK-8931 are ongoing, with completion dates set for July 2017 and March 2018, respectively.

Lilly’s first swing at BACE inhibitors saw toxicity problems, but the company remains in the field. The Phase II/III Amaranth study for LY3314814 (also known as AZD3293 via its partner, AstraZeneca’s, nomenclature) launched in December 2014 and lists a primary completion date as August 2019.

Amgen and Novartis have also agreed to share the risk around a BACE program, announced in September 2015, with CNP520 in Phase I/IIa and other preclinical candidates on deck.

The design of A-beta antibodies and BACE inhibitors is to strike AD at its molecular foundation, and thus has the potential to modify the course of disease. But some researchers argue that symptom alleviation is still important and, at the minimum, should be part of neurologists’ armamentarium, especially when contemplating the potential added therapeutic effect of cocktail regimens. Some drug developers see the singular bent to focus on disease modification as fallacious, and, hence, they believe the industry is disregarding or downplaying effective therapies that might bring value to AD sufferers and, with it, strong sales.

There is another gap in the research design for AD, best summarized by the question: why dissociate slowing the curve of cognitive decline from the larger effort to improve clinical outcomes? The question is posed by 30-year-old, former hedge fund wiz, Axovant’s CEO Vivek Ramaswamy, whose company brought in $315 million from venture investors in its June IPO. Axovant’s candidate, RVT-101, bought from GlaxoSmithKline for a cool $5 million, will start into a 1,150-patient, Phase III trial this fall in the US, Europe, and Japan. The Mindset
study promises to be a pivotal trial, as the company will leverage previous data from GSK’s attempts with the drug. Axovant is investigating RVT-101 on a stable background of Aricept (donepezil) to support its cocktail thesis and on recognition that symptom alleviation without halting neurodegenerative decline can still be beneficial for patients.

Another small firm making noise in AD and other neurodegenerative diseases is Anavex. The company’s Anavex 2-73 and Anavex Plus, a cocktail that adds donepezil, giving the therapy disease-modifying and symptom alleviation properties, is in Phase II. Early 36-day data is being presented this month, with 52-week, open-label data to follow. The company notes that by targeting sigma-1 and muscarinic receptors, believed through upstream action to reduce protein misfolding, it can alter A-beta, tau, and inflammation. The company has its sights set on Parkinson’s (PD) disease as well. Anavex has received an influential vote of support from the Michael J. Fox Foundation for this PD research. Also on board with the cocktail approach is Accera, which hopes to turn a supplemental/medical food into a late-stage AD pipeline candidate. AC-1204 is designed “to address the metabolic defect” of the AD brain, rather than more traditional A-beta and tau pathologies. Accera’s product induces mild ketosis in the body, supplying the brain with ketone bodies, which serve as “back-up fuel.” “We’ve shown that the brain can utilize ketone bodies and continue to metabolize, staving off symptoms,” said Accera CEO Charles Stacey. “It’s an increasingly well-established hypothesis,” he added.

Accera announced that its Phase III, 480-patient study, the first of two, was 75% enrolled in July and should be full by mid-2016. The trial is due to read out in the latter part of 2016 or early 2017. Accera will also launch its second Phase III study in 2016, which will be US and ex-US, said Stacey. With a history as a medical food known as Axona, Accera is coming from a unique place, considering the product was commercially marketed and has a substantial safety record. Recognizing that the medical food route is less known, in order to reach and benefit the maximum number of patients, the company is now focusing AC-1204 on the clinical pathway.

**Elsewhere in brain**

An advantage for pipeline technologies that target symptoms and/or more general aspects of neural decline is that they may also be applied to treat adjacent neurodegenerative disorders. Axovant’s second indication for RVT-101 will likely be Lewy body dementia, while Anavex lists epilepsy and PD as its next targets.

Acadia Pharmaceuticals chose to take on PD first. It’s drug, Nuplazid (pimavanserin), seeking approval for Parkinson’s disease psychosis (PDP) may also be applied to AD psychosis and schizophrenia. For now, the company has submitted its new drug application (NDA) for PDP, receiving breakthrough designation in doing so, a good sign that the FDA thinks its data is solid; it could issue a ruling in favor by May 2016.

Analysts believe that Acadia might need a big pharma partner to market Nuplazid if it wants to achieve peak sales that some estimate is in the $1 billion range; so far, the firm is choosing to go it alone. Reservations regarding the company’s lack of regulatory and commercial prowess were supported when the company postponed its NDA submission in March, stating the “decision to move back the planned submission is based on additional time required to complete the preparation of systems to support commercial manufacturing and supply and, in turn, to support FDA review.”

Also late stage for a new PD symptom reliever is Cynapsus’ APL-130277, a sublingual thin film formulation of apomorphine. The company is utilizing the 505(b)(2) pathway for the unique formulation of the drug that is already approved as Apokyn, a subcutaneous injection of the active ingredient marketed by US WorldMeds. Cynapsus initiated a Phase III safety and tolerability trial in September and intends to have data from that study, and an ongoing efficacy study, ready for NDA submission near the end of 2016. Apomorphine can help PD patients who experience “off” episodes rendering them unable to perform basic tasks like eating and getting dressed, making them increasingly reliant on assistance.

The company overcame significant formulation challenges to get the drug in the sublingual film, which it believes will pay off. Patients would be able to self-medicate as needed when they feel an “off” episode starting, a severe limitation of apomorphine in its current form.
**Cholesterol to collect**

In contrast to the frustrations and continued wait for better treatments in neurodegeneration, those in the field of cholesterol lowering are seeing a massive arrival of an extremely effective and highly controversial drug class. Big sales are expected, and payers are often portrayed as cowering in fear of the potential budget exposure. So far, however, sales are limited, negotiations are ongoing, and the perceived massive impact of the PCSK9 inhibitors has yet to be felt in full force.

Notably, pharmacy benefit manager (PBM) giant Express Scripts announced that both Sanofi/Regeneron’s Praluent, and Amgen’s Repatha will be on its National Preferred Formulary, ensuring that the drugs will reach the specific patient set who will most benefit.

One of the most volatile stocks in biopharma, currently hovering in the mid-$20s and with 52-week range of $18 to $120.96, is Esperion and the saga of its cholesterol-lowering pill ETC-1002. Esperion touts an impressive management pedigree: it’s founder and chief scientific officer is a co-discover of Lipitor, so the team knows the molecular pathway to lower cholesterol. Additionally, ETC-1002’s data has impressed the field, convincing most that the drug, which works upstream of statins, is an effective way to lower low-density, lipoprotein cholesterol. And lastly, amongst all of the strife of pricing the PCSK9 inhibitors has yet to be felt in full force.

Regardless of whether an approval can come soon, Esperion will launch a Phase III program for ETC-1002, the specifics which it will finalize by the first half of 2016. The trials will take a dual approach, evaluating the drug separately for “patients with statin intolerance, in addition to patients who are inadequately treated despite maximally tolerated statin therapy.”

Pfizer also plans to get in on the anti-PCSK9 market with bococizumab which is in Phase III trials. Key data could be available around mid-2016, with an approval late in 2016 or early 2017. Pfizer will have a lot of catching up to do, though some believe the antibody may gain market share if it can live up to the hype as a follow-on—but best-in-class—compound. In this regard, Lipitor’s own history as a fifth-in-class entry is instructive. Additionally, Pfizer will try to formulate a bococizumab pill and vaccine, the latter giving the potential for once-yearly dosing. The pill formulation could begin human trials by year-end.

Also banking on the benefits of a long-term cholesterol fix is Alnylam, with its partner The Medicine’s Company, on its Phase II-ready RNAi therapeutic, ALN-PCSc. The collaborators presented Phase I data in September and noted “highly durable effects with LDL-C-lowering lasting over 140 days after a single injection.” With The Medicine’s Company taking the lead, the group plans to start Phase II for the RNAi injection this year, with Phase III starting in 2017. Jefferies recently modeled peak sales for ALN-PCSc at $980 million, though it noted uncertainty given the early stage of the asset.

Cholesterol lowering has seen its share of clinical trial successes, with big sales revenue projected. But this fall also saw a failure leaving one whole class of pipeline candidates in limbo. Lilly’s...
stock cratered on October 12 with its announce-
ment that it was throwing in the towel on its
candidate, evacetrapib, a CETP inhibitor. Other
notables targeting CETP are Merck, with anace-
trapib, and TA-8995, which Amgen gained by
acquiring Dezima Pharma in September. That
compound could be written off, too. The CETP
space is littered with failures, and with the recent
Lilly revelation, the industry has been reminded
just how big of a risk they were to begin with.
The busted Lilly trial had enrolled 12,000-plus
patients, at considerable expense, having pursued
studies right up to Phase III.

**Oncology pairings**
The industry’s oncology pipeline is both wide and
dense, so it can be easy to lose the forest in the
trees. Complicating the picture is the fact that
combinations of various drugs are likely to start
making headlines with solid results. Rational,
time-efficient approaches to selecting which agents
will complement each other is going to be
invaluable as a competitive differentiator. And
the pricing debate over the bill for use of two or
more novel therapeutics simultaneously is des-
tined to follow shortly thereafter.

Immuono-oncology assets clearly continue to
draw the biggest crowd, whether you’re an oncol-
gist at a medical conference or an investor
watching the newest CAR-T company place its
IPO. Merck’s Keytruda (pembrolizumab) and
Bristol-Myers Squibb’s Opdivo (nivolumab) are
duking it out for PD-1 inhibitor primacy in sev-
eral cancer types, with patient subpopulations,
PD-L1 as a biomarker, and label language mak-
ing for compelling drama. Melanoma and lung
cancer are on the books, but the pipeline includes
expansion to more indications like head and
neck, gastric, breast, and Hodgkin lymphoma.
Analysts report that Opdivo could earn BMS
$8.8 billion by 2020 while Keytruda could bring
in $5.5 billion annually for Merck.

Though projected at sales of a measly $2 bil-
lion, Roche’s PD-L1, a successor target for
Roche’s atezolizumab could ultimately beat ana-
lyst expectations with its slightly differentiated
mechanism of action. The PD-L1 inhibitor rep-
resents a massive investment for Roche given its
11 ongoing or planned Phase III studies across
lung, kidney, breast, and bladder cancers.

Merck KGaA is partnering with Pfizer for the
PD-L1 inhibitor avelumab, which is in Phase III
for non-small cell lung cancer and Phase II for
metastatic merkel cell carcinoma. The two
pharma giants have said they will collaborate on
“up to 20 high priority immuno-oncology clini-
cal development programs with avelumab, many
of which are expected to commence in 2015.”

For BMS, adding Opdivo to Yervoy (ipilu-
umab) was an obvious combination of immuno-
oncology candidates, which predictively
improved progression-free survival in tandem,
versus solo treatment, while also upping side-
effect risks.

And this is where the potential for oncology
pipelines really gets exciting. A simple search for
combination efforts quickly becomes a compa-
nicating one with the many candidates already
progressing in place. But talk to any oncology spe-
cialist and they will stress that current possibilities
in immuno-oncology are just scratching the
surface. The science is in its early stages, having just
hit at a few checkpoint targets. But there are a lot
more, and with each new target, the potential for
new combination opportunities multiplies.

Deciphering which combos will be best for
which specific tumors will be a monumental feat.
Whether it will be the big pharmas throwing
massive resources at the problem to decode
tumors and rationally design treatments based
on specific tumor types or if small, more nimble,
more data-savvy firms will prove better at getting
there first—it’s a contest that will be interesting
to watch.

Back to the relatively simple pipeline concept
of developing monotherapies in oncology, one
potential blockbuster could come from Mille-
nium: The Takeda Oncology Company, with a
potential approval by early 2016. In September,
FDA granted priority-review status for the NDA
of ixazomib to treat patients with relapsed and/
or refractory multiple myeloma. Given the oral
delivery route for its proteasome inhibitor,
Takeda hopes the drug will do well amongst com-
petitors to help replenish revenue lost for its
blockbuster Velcade.

Looking to hit the market with a label for
double-refractory multiple myeloma is the Gen-
mab and J&J partnered drug daratumumab.
Janssen Biotech began a rolling submission in
June 2015 based on Phase II data and marketing
approval could come in 2016. Jefferies analysts
project $4 billion peak sales. Empliciti (elotu-
zumab), a multiple myeloma candidate from a
BMS/AbbVie partnership, has also received accelerated review and could gain approval in 2016. Also taking aim at an accelerated path is CTI BioPharma, with its Phase III drug for myelofibrosis, pacritinib. The company’s September press release noted that it was requesting the approval based on a single trial, which could drastically reduce the product’s time to market. The drug, like Incyte’s Jakafi, is an oral JAK inhibitor, but has specificity profile impacting JAK2, FLT3, IRAK1, and CSF1R, resulting in less thrombocytopenia and anemia, according to company statements. CTI BioPharma is comparing pacritinib to best available therapy in a Phase III myelofibrosis trial, but the company hopes it can gain approval sooner in patients with intermediate and high-risk myelofibrosis with low platelet counts. Analysts project global sales for pacritinib at around $750 million in myelofibrosis and other blood disorders.

**Biosimilars save in cancer, among other indications**

While most oncology developments combine great science and patient potential with sticker shock for payers, it’s also necessary to point out an emerging market opportunity in the US for major cost savings. One of the key pipeline events for 2016 will be the entry of biosimilars, according to AmerisourceBergen’s Grogg. “In 2015 the FDA approved the first biosimilar, Zarxio, and as we move into 2016 and beyond, others should follow suit.”

There are many factors to consider, specifically the fact that biosimilars will not have the same effect as generics. “An important consideration for manufacturers is the resources required to bring a biosimilar to market,” added Grogg. Biologic manufacturing is significantly more intensive and delicate than small-molecule generics, which are easily copied and thus able to offer immediate price reductions.

Also, payer-mandated switching is unlikely to occur immediately when the first biosimilars come to market because of uncertainty about these new products. “Biosimilar manufacturers will be required to conduct many of the same pre-launch activities as branded biologic manufacturers and would provide post-launch patient services to ensure uptake by physicians, payers, and patients,” Grogg explained.

**Zarxio’s initial price tag has been set at a 15% discount to the innovator product, Neupogen. As more biosimilars come through the pipeline, analysts expect deeper discounts in the 30-40% range. At 30% discount, gaining the equivalent of 30% market share, one analyst pegs the biosimilar’s revenues at $300 million per year.**

Sandoz has several biosimilars in its pipelines, including copies of pegfilgrastim, Epoetin-alfa, and outside of oncology into the biggest rheumatology moneymakers, adalimumab and etanercept, all listed as Phase III.

Plenty of other companies are developing biosimilar pipelines as well. Apotex could be one of the next to launch one, with its biosimilar version of Amgen’s Neulasta (pegfilgrastim), which it filed in December 2014. And Hospira, which is now part of Pfizer’s established products business, hopes to market Inflectra, a copy of Remicade as well as Remsima via its partnership with Celltrion—a match-up that illustrates how confusing the biosimilars market is becoming.

**Immune deals and break-ups**

Though biosimilars will be making an impact in the diseases of inflammation, clearly there is still much room for innovative products. One of the big buyouts from 2015 was Celgene’s $7.2 billion play for Receptos, gaining it the hot product ozanimod. Celgene’s announcement of the deal lists the oral, once-daily, S1P modulator as in Phase III development for ulcerative colitis (UC) and relapsing multiple sclerosis (MS). The company notes that the ongoing MS trials should have data in 2017, while data in UC could come out in 2018. Approval in MS could come in 2018. Celgene estimated peak sales for ozanimod in the range of $4 billion to $6 billion.

Other immune/inflammatory diseases like rheumatoid arthritis (RA) and psoriasis could see their pipeline of oral alternatives to its mainstay injectables grow. Pfizer’s JAK inhibitor Xeljanz (tofacitinib), already approved in RA, is striving to add indications, including UC, psoriasis, and psoriatic arthritis, where it’s currently in Phase III or under review. Pfizer did receive a complete response letter (CRL) last month for its supplemental new drug application for Xeljanz in psoriasis. The CRL is yet another snag for the drug, which has had sluggish sales since its approval in 2012; analysts believe Xeljanz could still hit projections in the $1.5 billion to $2 billion range.
The JAK inhibitor class will see several additions in the coming years that hope to distinguish themselves with slightly different safety/efficacy profiles. Lilly and Incyte’s baricitinib could give Xeljanz a run for its money. The companies announced that the pill beat out RA standard biologic Humira (adalimumab), though displacing TNF inhibitors in RA would be a tall order. A 2016 launch date is likely. Analysts believe it could reach sales of around $1.5 billion.

More in question is the future of Galapagos’ JAK inhibitor filgotinib. The drug is behind baricitinib chronologically, though claims for specificity and safety had some thinking it could be best in class. Galapagos’ partner, AbbVie, was supposed to escort filgotinib into Phase III, or buy it off Galapagos outright. Instead, the company pulled out this fall, prompting many questions about the future of the drug. AbbVie says it is now making Phase III plans for its own JAK inhibitor, ABT-494, while Galapagos is back to finding itself a dance partner.

Other inflammatory drama came when Amgen broke up with AZ over its IL-17 inhibitor for psoriasis, brodalumab. The drug was seen as a potential competitor to Novartis’ IL-17 inhibitor Cosentyx, which was approved for moderate-to-severe plaque psoriasis in January and could see peak sales of $4 billion to $5 billion. Suicidal thoughts in a clinical trial are never a good thing, though AZ’s CEO Pascal Soriot, during the company’s Q2 earnings call, said brodalumab was unlikely to be causally related to suicidal ideation. However, in September, the company announced it was calling it quits as well, and auctioned the drug off to Valeant for $100 million, subject to $245 million in milestones and bonuses.

**Rare competitors**

Developing drugs for orphan diseases is clearly not a fad. With 7,000 rare diseases and 250 new ones identified each year, there is clearly room for growth; companies are attracted to the space, where there’s generally less competition in a given...
RARE DISEASE
DUCHENNIE MUSCULAR
DYSTROPHY

**Drug Name:** Translarna (ataluren)
**Company:** PTC Therapeutics
**Phase:** III
**Catalyst:** Submit NDA year end
**Estimated Sales:** $900 million

**Drug Name:** Drisapersen
**Company:** BioMarin
**Phase:** Submitted
**Catalyst:** Year end
**Estimated Sales:** $1 billion

**Drug Name:** Eteplirsen
**Company:** Sarepta
**Phase:** Submitted
**Catalyst:** Year end
**Estimated Sales:** $2 billion

**Drug Name:** Resunab
**Company:** Corbus
**Phase:** II
**Catalyst:** End of 2016
**Estimated Sales:** $2 billion

Disease. Additionally, earning an FDA priority review voucher for successful development in a pediatric condition is a nice added benefit.

However, Duchenne muscular dystrophy (DMD) is one rare disease that has formed a bit of a crowd. This spring, BioMarin beat Sarepta by mere weeks in submitting its drug, drisapersen, before Sarepta’s eteplirsen, and a decision may come out simultaneously before the end of the year. Both drugs utilize exon skipping of exon 51 in the dystrophin pre-mRNA, which could result in a treatment for approximately 13% of DMD sufferers. The two companies have been unusually combative in their interactions and have expressed interest in buying other companies to establish the premier DMD brand that could evolve combinatorial treatment regimens.

Slightly adjacent, PTC Therapeutics’ Translarna (ataluren) targets a different 10% of patients with nonsense mutation by permitting readthrough of a premature stop signal. The company has struggled to show significance in a crucial clinical endpoint, the six-minute walk test. A late Phase III trial showing a 15-meter improvement failed the bar of statistical significance; however, meta analysis of data and observations in a prespecified group of boys should be enough for approval, says company executives. PTC is planning to initiate the rolling NDA submission by the end of the year. Because of its nonsense mutation targeting mechanism of action, PTC is also testing Translarna in nonsense mutation variants of cystic fibrosis (CF), in Phase III and could progress it in mucopolysaccharidosis I.

Translarna could peak at $900 million in European and US sales, with a projected $300,000-a-year price tag. Peak sales estimates for both drisapersen and eteplirsen range from $500 million to $1 billion a year.

Collaborating with cutting edge science are Isis Pharmaceuticals and Biogen, whose antisense drug, ISIS-SMNRx, is in Phase III trials for infants and children with spinal muscular atrophy. Data is expected in 2016 or 2017, and sales could approach $2 billion, according to one analyst’s estimate based on a patient population of up to 35,000 in the US and EU, at a $125,000 price tag and 50% penetration.

Rather than developing a rare disease drug from the ground up, Corbus Pharmaceuticals has taken a different approach by finding potential rare disease gold in a defunct pain asset. Resunab is listed in Phase II in rare inflammatory diseases CF, systemic sclerosis, and dermatomyositis. After receiving support from the Cystic Fibrosis Foundation, Corbus could rival Vertex in the CF space, with potential annual sales of $2 billion.

**The next gen: Pipelines that don’t look like pipelines**

Looking at deep R&D trends, there is potential that pipelines in the future may not all look like what companies display on their websites today. If the trends for organizations to focus on topics like “wellness” and “aging as an indication” continue, it’s tough to see how the Phase I to III chronology can be realistically applied.

Alector is one company taking a novel approach to AD, seeing it as an immune disorder at its core and believing that what immunotherapy is doing for cancer, they will one day do for neurodegeneration. The notion has some early support, with a $32 million Series C funding in September and some impressive names in its investor syndicate such as OrbiMed, Polaris Partners, Google Ventures, Topspin Partners, and Mission Bay Capital.

Calico is bringing the full force of Google into the aging arena, and investors and patients alike hope to see a promising pipeline develop. But, clearly, proving a treatment that is workable in aging will necessitate trials with unprecedented challenges in terms of design, scale, and, of course, the productive interpretation of mind-boggling amounts of data.

**A new business: Being well**

Regardless of whether aging and wellness represent not just new indications but entirely new branches of medical science, it will be incumbent upon industry R&D departments to take up the technology tools and human expertise necessary to develop products for the space. For example, for wellness to ever go beyond “self-help” and dieting fads, really big data will have to be applied and therapies will have to be able to address the complex needs of individual patients, including their genomes and microbiomes, and all co-morbidities and behaviors, too. Mastering these emerging fields provide the opportunity for an end to the cyclical ups and downs of conventional acute care drug discovery by getting much closer to what patients really need to stay healthy, across a much longer lifespan.
The Urgent Push for a Pull Supply Chain

Experts warn that if pharma doesn’t take a tighter grip on its supply chain and yank it into the 21st century, the industry could soon face distribution and logistics crises on an unprecedented scale.

By Julian Upton

In Pharm Exec’s 2013 end-of-year supply chain roundup, we began with a three-word vision of the immediate future that left little room for ambiguity: “Serialization is coming.” With the impending laws regarding “track and trace” promising to alter the way pharmaceuticals are packaged and shipped, we outlined how global pharma was gearing up to deal with the effects of serialization, and how companies needed to review their own internal practices and those of their outsourcing partners, as the need for technology solutions for both sides of the outsourcing relationship became more evident.

Of course, that message still stands, and it is arguably even more urgent if we are to believe Ian Haynes of 3C Integrity Consulting, who unnerved many in the audience at London’s recent FlyPharma 2015 conference when he said that pharma is still not ready to meet the obligations of track and trace. But since 2013, a number of other concerns—some equally as transparent, others less immediately visible—have emerged to stand alongside the move to serialization as potentially major disruptions in the way the industry operates. Indeed, as we head into 2016, one industry insider believes the pharma supply chain is facing a confluence of challenges “the likes of which it has never seen before.”

Daunting path

Alan Kennedy, director at PartnerSave, pulls no punches when he outlines the litany of challenges that he sees confronting the pharma supply chain over the next five years. He points to “the escalating good distribution practice (GDP) demands on the industry (and the need for greater harmonization); the pressures from the marketplace for cheaper medicines; shifting consumer expectations, with the trend towards more specific, personalized medicines; and rocketing costs.”

The crises are already starting to hit. Kennedy says: “A lot of pharma companies are waking up to the fact that they need to sharpen up their act in terms of compliance with the regulations. But while a lot of the need for change is regulatory driven, it’s also competitive. There’s a lot of lip service paid to the need for reform, but the problem is translating the intention into action.”

One of Kennedy’s “perfect storms” on the horizon is gathering around outsourcing from, and supply to, emerging markets. As these are the markets “where growth is coming from,” he stresses that pharma companies must be better integrated and work more closely with their partners if they are to continue to expand in developing countries. “They’ve got to make sure that the best practices that apply here also apply there. There’s no use having a state-of-the-art facility in the US but not in, say, India or Latin America, where you’re doing business; products have to be reliably protected from start to finish.”

John Menna, vice president of strategy, healthcare logistics, at UPS, often observes companies “doing a fantastic job of maintaining the efficacy of their products from manufacturer all the way to the destination...
country.” But when the products get to their destination, where there isn’t the same commitment to rigorous procedures, “they end up not being stored at the proper temperature, in the right environment, and with the right protocols.” And companies may be unaware of this, Menna adds. “If a vice president of supply chain at a big Pharma company flies out to the destination and sees how products are being stored there, they may be in for a shock. Companies need to take a hard look at their supply chain endpoints, and at the providers that they’re using.”

Fast-growing firms must establish their emerging market networks in a “much smarter, more flexible way,” Vitaly Glozman, partner at PwC, told Pharm Exec. Traditionally, big Pharma’s “huge, static networks” have been difficult to change or use effectively. Glozman believes that a “hub-and-spoke” model could provide the key. “By investing in a hub in, for example, Dubai and then outsourcing the hub’s ‘arms and legs’ to local distribution warehouses across the Middle East, a company can minimize its CAPEX investment and achieve flexibility,” he explains. “Or, if things go south, it has the ability to reduce volumes and spend, kind of like transitioning its CAPEX to its OPEX.”

As companies gear up to expand into more countries with more products, however, there will be, accordingly, more threats to data and product security. “A lot of companies are going to be selling so-called drug-device combination products that include data collection capabilities. These products will enable the patient to communicate the results. How that data will be transitioned back to the pharma company or provider presents a big challenge.

Companies will not only have to deal with product security but also patient information security,” says Glozman.

The patient ‘pull’

Certainly, pharma seems somewhat unprepared for the supply chain demands of an increasingly patient-focused future. This is largely a result of the healthcare supply chain remaining, says Menna, a “push” supply chain, where manufacturers, wholesalers and distributors push products into the channel and downstream to the hospitals, doctors’ offices and ultimately to the patient.” But things are moving to a point where patients are pulling products through the supply chain for their own consumption. “This is similar to a retail environment; to take an extreme example, it’s like an online purchase of audio-visual equipment to be delivered to the home.”

With more personalized medicine procedures being done outside the institutional setting and closer to the patient—either in an outpatient facility or even patients’ homes—logistics solutions will need to start providing for the patient—either in an outpatient facility or even patients’ homes—logistics solutions will need to start providing for the sending of alerts to patients, allowing them to determine when and how a product is delivered, and facilitating the transportation of critical specimens from the patient to diagnostic labs.

Data: Key cog in chain

As the pharma supply chain evolves from “push” to “pull,” analytics will become a more vital part of the process. Much has been written about analytics and big data, but now more than ever, leveraging the data that pharma has been collecting and investing in predictive and prescriptive analytics will be key to maximizing the promise of data, for issues ranging from temperature tracking to warnings of drug shortages and recalls. “You’ll start to see companies making more use of big data to develop better therapies and leaner supply chains in the next five years,” says Menna. The challenge of analytics begins with determining the different business questions you want the data to answer, Glozman says. “Otherwise, analytics is a very strategic tool that can be misunderstood and misused.” He goes on: “You need bright, capable people managing your supply chain. You don’t just want people who say, ‘Let’s do some analytics.’ They need to say, ‘Wait a second, what is the specific problem we need to understand better? Let’s identify the data attributes and then define our analytics.’”

For Kevin Pegels, VP, global supply chain management – PS Biotech, Bayer HealthCare, there are ongoing issues around end-to-end data availability and decision-making that also need addressing.

“There is a gap right now in pharma with regard to the visibility of data concerning suppliers’ capacity and inventory and customer inventory,” he says. “What inventory do customers have? What is patients’ consumption? This information is critical for an efficient supply chain.”

Non-pharma lessons

Pegels formerly worked in the consumer packaged goods business, which he says “is about 15–20 years ahead of pharma in terms of best practice supply chain management.” He points out that as soon as consumption is seen, for example, at a Walmart store, that immediately drives orders to the suppliers for replenishment shipments to the Walmart warehouses. “Pharma is long way from that kind of end-to-end visibility, but it is catching
“There is a certain level of urgency, because we are talking life or death, or at least quality of life.”

“An integrated supply chain is more than just a collection of collaborative organizations,” he notes. “If you look at it as a box, within that box you’ve got all the network controls and tools: quality management, shipment visibility, inventory management, regulatory compliance, network communications, education, and training. A properly integrated supply chain addresses all these issues as a unified network.”

For Glozman, cost will become key. “I believe there’ll be a push for the lowest common denominator in terms of cost. I don’t think companies have yet begun to address this issue properly. Bending the supply chain cost curve is going to be critical.” Glozman also sees more focus on collaborating with regulators. “The industry still currently deals with the regulator as a separate entity rather than as a collaborator,” he says. But with so many changes looming over the next five to 10 years, certainly as far as manufacturing technologies are concerned, “the industry will change to have a much more collaborative relationship with regulators.” Similar to what has taken place in other regulated industries, Glozman sees pharma companies “actually co-locating a regulator staff member within their facility and working with them on new product development.”

The industry “is currently about 30-35% over capacity and it will take a little while to subsume this, because some of this capacity is not ready for the future,” Glozman adds. There will be “a lot more flexible, single-use manufacturing, particularly for complex and biologic products where companies want to minimize the cross-contamination risks.” For more high-volume manufacturing, he adds, “I think we are going to see continuous manufacturing become more of a standard over the next five years.”

Better leveraging of end-to-end data and decision-making will shorten lead times within the pharma supply chain, says Kevin Pegels. He also sees supply chain management gaining more stature within pharma companies. “You may see a chief supply chain officer reporting to the CEO in the next five years,” he says. “With all the competition and downward pressure on pricing, the supply chain needs to play a bigger role to maximize cost efficiency. And just to be part of the game with customers, companies have to have reliable and predictive supply. Pharma is realizing that it has to start investing now.”

Against the clock

The time the industry has to re-engineer its supply chain is hardly in abundance. Is such a revamp of current practices achievable in such a relatively short time? Despite his concerns for the future, Alan Kennedy, for one, is confident that “there’s always someone to take the lead, and some companies will do that. Once that happens, they will see a big competitive advantage coming in their direction. They will see quality improvements, profitability improvements—all the advantages that come with better integration.”

Maybe then pharma’s supply chain reaction will start in earnest. 

OWN INNOVATION IS VITAL

Given those dynamics, pharma still needs to find its own solutions for its own supply chain challenges. The “big answer” for Kennedy is that companies have to start integrating more successfully.

Outside of consumer packaged goods, which other industries can pharma look to for lessons on optimizing the supply chain? Alan Kennedy notes that one industry that has been a big advocate of supply chain integration for the last two decades is construction.

“The construction industry has the disadvantage of having one of the most complex supply chains out there,” he says. “Every project is a one-off, every project needs a different supply chain, and every one is organized in a different way, all for relatively short periods of time. Construction has all sorts of challenges that are driving real, close collaboration.” The automotive industry’s supply chain management also “is right at the forefront,” says Kennedy, along with retail and electronics.

But while best practices from other industry supply chains can be adopted by healthcare, “it is very important to note that healthcare is different,” says Menna. “The first thing to remember is that at the end of the healthcare supply chain is the patient, whose quality of life will be affected, and hopefully improved, by the treatments he or she receives. So there is a certain level of urgency, because we are talking life or death, or at least quality of life.”

Second, the sensitivity of the products and the regulatory environment surrounding their movement and storage “are unlike anything in any other industry.”

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In the past few years, we’ve seen the biopharmaceutical industry begin to shift from a one-size-fits-all blockbuster approach toward an individualized, precision science model. This transformation has propelled companion diagnostics (CDx) into playing a more critical role than ever in the commercialization of biopharmaceutical therapeutics. Therapeutic (Rx)-CDx pairings are in development or have already launched in multiple therapeutic areas—including cardiovascular (CV), CNS, inflammation, oncology, and virology—and this is expected to continue across most other disease states.

As a point of reference, between 2012 and 2015, the FDA approved approximately 30 new targeted therapy approvals and more biomarker-driven treatments on the horizon, properly commercializing biopharma drugs paired with a companion diagnostic can be a competitive differentiator. Four “can’t miss” strategies for successfully managing the development, launch, and commercialization of Rx-CDx pairings are outlined here.

By Jeff Liepman, Kevin Barnett, Kun Lee, and Nathan Lyman
therapies (treatments that more precisely identify and attack damaged cells or pathways), many of which benefit from a CDx pairing. In 2014 alone, eight of the 41 novel drugs approved were biomarker-directed therapies. The significance and frequency of biomarker testing is rising across the industry, based on a heightened focus on—and advancement of—our understanding of genomics, identification of potential drug targets, and continued development of biomarker-associated therapeutics.

With this transforming environment comes opportunity. Successfully managing the development and commercialization of Rx-CDx pairings has become a source of competitive advantage for biopharma and diagnostics manufacturers alike, yet it requires a unique and innovative approach. In this article, we outline four “can’t miss” requirements for realizing success in commercializing Rx products paired with a CDx:

1. Rock-solid CDx landscape understanding
2. Symbiotic biopharma and diagnostic partnership
3. Pressure-tested Rx-CDx development approach
4. Integrated Rx-CDx launch and commercialization planning

Grasp of landscape
To stay ahead of the curve in personalized medicine, it has become increasingly important to hold—and act on—an informed position regarding events playing out in the CDx market, just as any manufacturer would in Rx. If upstream assumptions about the market are off base or outdated, so will be the resultant strategy. To further drive this point home, many significant aspects of the CDx market are changing in the very immediate term, as demonstrated below:

» Biomarker testing has historically been a one-off, expensive and narrowly focused intervention (i.e., only testing for one gene or protein). This is changing with the advent of multi-plex testing and next-generation sequencing (NGS), promising a higher throughput and more comprehensive analyte read-out. Select manufacturers are getting involved through innovative cross-industry collaborations. For example, two primary NGS consortia include: 1) Thermo Fisher with Novartis and Pfizer, and 2) Illumina with AstraZeneca, Janssen, Sanofi, and Merck Serono. Many biopharma companies that have not yet sought or committed to a particular NGS consortium are evaluating which path to take. NGS is a potential game-changer for players in CDx and opportunities to collaborate on the technology may likely impact future clinical and commercial success rates of Rx-CDx pairings.

» Historically, many Rx-CDx stakeholders have benefited from the utilization of laboratory-developed tests (LDTs). For example, reference labs were able to maximize revenue by developing their own “home-brew”—or LDT—tests at a fraction of the cost larger Dx companies would charge. Payers and patients would also benefit from more cost-efficient lab economics. This, however, is likely to change as the FDA is increasingly implementing more stringent rules on what tests will be included in an Rx label. The FDA recently published LDT guidance in an attempt to enforce the changing regulatory requirements of LDTs. This is a significant milestone following its release of the “preliminary” guidance on LDTs in 2011.

» Changes with LDTs also have implications for how payers may (or may not) cover such Rx-CDx combinations moving forward. Ultimately, testing laboratories have begun means, such as blood/serum testing, and tailoring promotional efforts to new or different customers like pathologists and surgeons, as opposed to just prescribing physicians. Such changes may introduce new channels for marketers to consider and unique commercial scenarios altogether (e.g., brand decision-making at time of sample testing).

Manufacturers that have an informed perspective on CDx and recognize the value of pinning commercialization strategy to both Rx and CDx market insights are likely to fare better with their launch effort.
encountering financial difficulties with declines in reimbursement and possible elimination of payment for LDTs, which has been one of their core sources of revenue. As laboratories are pushed out of business or restructured, Rx-CDx manufacturers are being challenged to find new ways to ensure tests are pulled through and paid for altogether.

Many other aspects of the CDx marketplace such as coding, regulatory pathways, systematization of test scoring, and standardization of testing protocols will undoubtedly continue to evolve.

It’s unlikely that any one market report or research effort will provide the perfect CDx market backdrop or set of assumptions, especially considering things will continue to change. However, manufacturers that have an informed perspective on CDx and recognize the value of pinning commercialization strategy to both Rx and CDx market insights are likely to fare better with their launch effort and have more success in addressing difficult tradeoff decisions that will inevitably need to be made throughout development and launch (e.g., co-develop with FDA-approved current CDx platform or take a shot on an unproven, yet potentially more sensitive, new platform).

Symbiotic partnership
Biopharma and diagnostic companies are often at odds when it comes to topics such as culture, incentives, and business models. For example, diagnostic companies have historically operated with fewer compliance hurdles, smaller budgets, less rigorous clinical trials, and shorter timelines than their pharma counterparts. Not surprisingly, diagnostic firms care greatly about maximizing utilization of their tests—regardless of resultant therapeutic choice or utilization. However, biopharma companies prioritize maximizing product utilization, regardless of test used. While both scenarios conflict, neither party would be successful without the other.

Another important aspect of any Rx-CDx partnership includes the nature of the diagnostic company itself. Is the diagnostic company an in-house division of the biopharma company (e.g., Roche/Roche Diagnostics)? If not, will the biopharma team seek to in-license an existing approved test or simply partner with an external diagnostic company? Each unique biopharma and diagnostic partnership scenario will foster different opportunities and barriers to be considered and addressed. In short, the key then becomes how to best design a mutually beneficialRx-CDx partnership and operating protocol based on what scenario makes the most business sense.

A good starting point with any business collaboration is to define and align on business objectives and goals for the partnership. An example might be to “maximize identification of eligible patients for a therapy by using the best available test.” It’s also important at the onset to establish an operating protocol with both parties by defining and documenting items such as working principles, roles and responsibilities, shared timelines, and governance. Ongoing management of and feedback on the operating protocol might be handled by a joint steering committee with mutual representation. There’s also great value in outlining the expectations and plan for collaborating on key strategic decisions and milestones throughout development.

One of the more complicated—yet unavoidable—aspects of Rx-CDx collaboration is value and incentive sharing. We encourage collaboration partners to define an incentive plan that motivates both parties to resource and deploy their respective development efforts in parallel. If incentives are not objective, attainable, or equitable, it is unlikely both parties will be motivated to work symbiotically with one another.

An additional consideration for many companies is how they approach exclusivity with their product and/or test. The FDA is becoming increasingly specific with its Rx-CDx requirements, to the extent that 1) only FDA-approved tests are in the label and 2) specific tests are appearing or referenced in the label of approved therapeutics (e.g., Tarceva and the cobas EGFR Mutation Test). Partnering organizations will need to research and agree on whether there is mutual interest and rationale for establishing exclusivity agreements (or not) at an early stage in development in order to minimize the potential for downstream disturbances.

Development approach
Identifying and incorporating an optimal assay (i.e., one that is technically feasible and commercially viable) early in the drug development process will save many headaches further downstream. In this section, we will discuss elements of establishing an effective Rx-CDx development approach.

It’s important to ground an Rx-CDx development strategy on early alignment of shared objectives, deliverables, and milestones. Once a biopharmaceutical manufacturer has verified the need for a CDx, it’s essential next to evalu-
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ate if CDx co-development should occur in-house, be in-licensed from existing FDA-approved assays or platforms, or be done in partnership with an external diagnostic development firm—such as a contract diagnostic organization (CDO). Each scenario will have cost/benefit tradeoffs.

Biopharma organizations with an in-house diagnostics division (e.g., Roche, AbbVie) often have the advantage of managing their own integrated Rx-CDx development processes and decisions; however, even they are still seeking creative ways to improve their development capabilities and organizational efficiencies. The many challenges and requirements noted in this article are—without a doubt—applicable to the larger and more experienced Rx/CDx corporations as well as the smaller players.

After identifying and evaluating the appropriate pathway for co-development, potential areas for alignment between the Rx and CDx arms should be defined and reviewed collaboratively. These areas of alignment might include items such as timelines, cost-sharing milestones, governance (business objectives and incentives), business model gap identification, regulatory and labeling requirements, and launch-readiness expectations. It’s incredibly important to note that a successful Rx-CDx co-development experience may result in higher clinical trial success rates and optimized development timelines (which also translates to cost efficiencies). Authors of a recent study of 676 non-small cell lung cancer (NSCLC) trials observed that biomarker identification, incorporation, and planning increased success rates by more than 50%, with trials completing in less than half the standard time.

Contrary to a seamless co-development experience, potential pitfalls throughout development can drastically diminish success rates and product value if not avoided. One of the more common pitfalls is that the Rx collaborator may be focused on one lead asset while the Dx partner may be focused on a broad set of tests, diseases, and platforms. This can lead to disproportionate development investments and efforts and maligned timelines between the two companies—all the more reason that a shared vision and subsequent planning integration in development processes is key. Pitfalls will inevitably play out differently for each company and development technology; however, having an objective team or a partner on both sides with experience in Rx-CDx development and a willingness to truly collaborate is crucial to avoiding or mitigating such stumbling blocks.

Rx-CDx co-development processes require are likely to differ across therapeutic areas as well. For example, oncology is arguably the most developed, understood, resourced, and applied therapy area for CDx today. First, the idea of personalized medicine is incredibly important and applicable in oncology since the disease itself is unique to every patient. Oncology offers many clear advantages for the co-development of a CDx. Early and proactive CDx incorporation during Rx development will often reduce trial costs through more efficient patient selection and expedited timelines; it may also increase success rates based on a more specific and responsive population (patients tend to respond positively to such data). A great example in oncology would be Pfizer’s Xalkori, indicated for ALK-positive metastatic non-small cell lung cancer (mNSCLC). mNSCLC is a crowded and tremendously high budget-impact market, but early ALK+ testing has many benefits: it identifies EML4-ALK translocations if present, improves ALK+ patients’ outcomes by treating the underlying genetic alteration, and potentially saves on treatment cost for payers by screening for and selecting a smaller subset of patients who are likely to receive benefit from Xalkori, since only 5% of mNSCLC patients exhibit EML4-ALK translocation. Working up to launch, Pfizer had primed the market with unbranded campaigns targeting various stakeholders (e.g., oncologists, pathologists, patients/caregivers) to not only raise the awareness for ALK testing but to drive demand through both “pull” and “push” strategies. Other examples of best practices Pfizer deployed to support its Rx-CDx launch were as follows:

### Commercial Strategy

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**Key Rx Development Stages**

<table>
<thead>
<tr>
<th>Discovery/Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Regulatory Filing/Approval</th>
<th>Rx Launch</th>
<th>Post-Launch</th>
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<tbody>
<tr>
<td>Biomarker identification</td>
<td>Clinical testing and development</td>
<td>Clinical validation</td>
<td>Clinical trials</td>
<td>Clinical trials</td>
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<td>Clinical trials</td>
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**Rx-CDx Collaboration Opportunities**

- Translational research and development
- NDA submission
- Clinical trial design
- Companion diagnostic development
- Clinical utility
- Analytical validation
- Clinical trial design
- Analytical validation
- Clinical trial design
- Analytical validation
- Clinical trial design
- Analytical validation

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Producing a strong commercial strategy for a Rx-CDx development is a key element in realizing success at launch. It is important that such decisions be made jointly—for example, the value proposition of the Rx-CDx or how the CDx will be incorporated into the Rx target product profile. It’s important that such decisions be made early and incorporated into both Rx and CDx launch plans. Myriad other activities and work plans are specific to Rx or CDx, but both companies would benefit from sharing them, nonetheless. The framework of an Rx-CDx co-development process, as well as key collaboration opportunities are noted in the figure on facing page.

Another collaboration opportunity includes sharing and aligning on field force objectives, strategies, and call planning so as to prevent account overlap or conflicting messages. With respect to access and reimbursement, consistent and integrated value strategy and messaging by Rx and CDx counterparts are key to securing adequate coverage with payers. Both organizations should consider the impact of things like bundled payments, contracting/rebates, and price increases for the therapeutic and diagnostic, informed by feedback from a variety of payer organizations.

Lastly, mutual learnings and data should be shared across organizations. Whether it is market research, investigator feedback, or demand forecasts, there will be plenty of opportunity to inform one another on key aspects of launch strategy and planning as they relate to the Rx-CDx agreement. The expectation is that better alignment on market and planning assumptions will help prevent potential misfires or distractions as the Rx-CDx approaches the market.

**Keeping pace**

The advent of precision medicine is playing out before us. Biopharma companies that desire to realize true value from CDx and maintain or establish a leading position with their technology will need to ensure they’re getting the most from their commercialization approach. More specifically, involved organizations will greatly benefit from learnings and insights gathered from development and commercialization of Rx-CDx technologies in the past and should proactively consider and plan around the many expected strategic and operational challenges associated with developing personalized medicine technologies.

Understanding the broader landscape of the Rx-CDx environment will also help guide organizations in determining what type of partnership is best for them or their assets and what planning will be required to maximize success at launch. It is our belief that developing and executing an Rx-CDx commercialization approach that addresses the four “can’t miss” requirements noted herein will provide manufacturers a tremendous head start in attaining a competitive edge in the burgeoning field of precision medicine.

**Integrate launch, commercialization**

Delivering on regulatory requirements, reimbursement hurdles, and a strong commercial strategy for a therapeutic and test requires careful parallel processing. Both an Rx and CDx require diligent planning leading up to launch, plans that typically contain distinct timelines, separate regulatory milestones, and an order of magnitude difference in resource dollars. So how can both assets be developed and prepared for launch in parallel?

The key here is early, proactive, and transparent communication between partners. The content expertise required for Rx and CDx launch planning and execution is best left in the hands of each organization; however, it is never too early in the partnership to align and/or merge launch timelines and plans. A number of important decisions should be made jointly—for example, the value proposition of the Rx-CDx or how the CDx will be incorporated into the Rx target product profile. It’s important that such decisions be made early and incorporated into both Rx and CDx launch plans. Myriad other activities and work plans are specific to Rx or CDx, but both companies would benefit from sharing them, nonetheless. The framework of an Rx-CDx co-development process, as well as key collaboration opportunities are noted in the figure on facing page.

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Think Globally, Act Locally
The best approach to getting global brand campaigns to work all over the world

There is a paradox at play in the world of global marketing. We live in an age where the expectation is that messages can be shared instantaneously across the boundaries of time, language, and location. We are more connected than we have ever been, yet we still are not a unified world. What motivates us, what inspires us, and what drives a brand to succeed is vastly different between continents and cultures. Yet we talk about “globalization” as if that undertaking is possible in a meaningful way with our physicians and patients around the world.

The goal in marketing global brands is to seek the highest common denominator in verbiage that can resonate with targets despite their location or culture. So as we begin to think about global launches, we focus on our message, the mix of media, and the journey of decision-making as expected.

What has changed is the speed and tolerance of what the world is willing to wait for. We now have the capacity with the click of a button to disseminate our message all over the world, instantaneously. But as marketers, we know the path from globalization to localization is an important one, in which steps can’t be skipped. So what are the keys to getting a global message to become a local message in today’s digital world?

Position the brand to address a global unmet need in a local way
Global marketers are challenged by this every day—how to make a single item or molecule own the same position in markets that have vastly different landscapes. For some, the first reaction is to retrench into the boundaries of their role—“it’s my job to be consistent and create a single great campaign, and it is the local team’s job to adapt.” To some extent, this is true, as the global marketer is the owner and champion of the brand. However, when we expect the local teams to take our carefully crafted, often Western-oriented, English-centric position and deliver it as a relevant local position, we often see things start to unravel.

A common blind spot for global marketers, especially those new to the global role, is to focus on the product, competitors, and the message itself and not on the environment (government or payers) in the markets they are serving. For example, a product may be best in its class and it treats a condition better than any other alternatives. The manufacturer has spent a significant amount of its launch budget on positioning, testing, and creating a killer campaign. The company sends this campaign and related assets to its regional or country affiliates, the global marketer is the owner and champion of the brand. The company sends this campaign and related assets to its regional or country affiliates. Brand teams test the campaign and make adjustments to it based on feedback.

The response the manufacturer gets, however, is disappointing. It turns out that the campaign it just finished is seen by some regions as a cure to a disease not considered debilitating enough to warrant advanced intervention. The doctors agreed that it would be a “nice to have,” but they don’t need it, and, furthermore, their governments won’t pay for it. For example, in surgical ophthalmology, there are differing opinions on how astigmatism should be treated around the world. For some markets, treating the problem surgically is the answer and for others, they rely on glasses. Although a surgical approach may yield best patient outcomes, not every market sees the “need” the same way. Often, a manufacturer is not simply changing techniques, but is asking to change mindset—which is, of course, a much greater challenge. So how to avoid?

Get buy-in—early and often—from affiliates around the world
Strong global marketers know this, and it is a natural part of their process. Sadly, it is still not the norm for most companies. For many multinational companies, the global marketer is expected to deliver within the timelines of the launch project and accelerate everywhere possible. Eliminating additional rounds of positioning feedback can shorten a project cycle significantly but does so at significant risk. It takes a courageous project manager (PM) to hold up a project or delay a milestone date in order to get sufficient affiliate feedback. But if the reasoning is unimpeachable and the benefits made clear, the PM may be creating a short-term pain for a long-term gain. A few weeks of delay and a great launch trump a rushed launch and months of delayed revenue, every time.

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A deep understanding of a company’s strategic markets and launch schedule will create the guardrails of its affiliate feedback plan. It is important to clearly outline decision points within the project plan where feedback is critical. From there, determine which feedback needs to be weighted more. Which country launches first? How quickly will the brand launch in the next country or cluster? Which positioning will provide the biggest return in these countries? Is the manufacturer the first everywhere, or is it jumping into some highly competitive markets? The positioning should match the best overall return potential but can also evolve over time. Some marketers will balk at this, but we have all done it—whether it’s called “evergreening” or “market realignment,” very few products live their entire lifecycle with a single position.

A positioning that hits the mark for Germany may not be right for Japan. However, since many products are not launched in Japan until several years after introduction in the European Union (EU), will that time allow for a change in positioning globally? Or should a company consider multiple positions to satisfy these important markets? This used to be marketing heresy, but we have all done it—whether it’s called “evergreening” or “market realignment,” very few products live their entire lifecycle with a single position.

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How can a brand team accomplish this, however, without sacrificing speed to market? Regular live discussions are a good start, but the nature of global positions is that a brand will rarely be in one place the entire year. We have to utilize technology to efficiently deliver materials for review across time zones, and be well-prepared prior to those live discussions taking place. A centralized means of sharing ideas and assets that can be quickly vetted through local legal and regulatory teams will also increase a marketer’s potential for high-speed reviews and feedback sessions.

**Develop a digital tool that enables global-to-local with a few clicks**

The ongoing challenge global teams face beyond the boundaries of time, location, and language is asset management. Most companies develop global campaigns and then distribute them, with fingers crossed, through their global affiliates. But often, some places in the world need to either 1) localize the message to their targets or 2) translate, rethink, or even reimagine some of the materials they need to be successful in their market.

We often see companies create beautiful, integrated campaigns that are well-received in US markets, but then are rarely used outside the US. It is not that the agency and brand teams failed, but rather didn’t give each market the freedom to adjust the messages and tactics based on their needs in a cost-effective and quick way. So they sit, unused, on e-brand websites.

To solve this, companies are developing digital asset managers that will allow every user with a “seat” around the world gain access to assets and be able to customize them in real time. We have even found a way to connect the development of customized assets that can be regulatory/legal/medical reviewed at the local level, after they have been reviewed at the corporate level. Even better, these tools can be translated in the market, and the region can own the “big idea” the campaign worked so hard to achieve but still be able to localize and build a version of a sales aid or digital tool based on the needs of their targets, regardless of where they are. This saves time and money and enables a product to maintain the integrity of the global brand position, but allows regions and market to execute on a local level.

In order to globalize a brand, the manufacturer must have a message that is consistent and meaningful. It needs to find a way to position the brand so that it is important but not isolating. Marketers should talk to their global affiliates and ask for their input; but, most importantly, find a way to get its hard-earned message to the world in a way they will use it.

So many global campaigns are like custom homes that no one ever lives in—they are built for all but used by so few. Using a collaborative approach to developing a brand message and then launching it in a way that enables rapid localization can help ensure that your beautiful house has its share of visitors who come back often and stay a while.
Market Access Reinvented

The key steps to implementing the "patient access" model of the future

When Baxalta Inc. separated from Baxter on July 1, 2015, the company had a unique opportunity to design and build from the ground up the market access capabilities required to succeed as an independent, $6 billion biopharmaceutical business. Baxalta looked ahead five years to what it envisioned were the trends in the industry, defined value from the perspective of those influencing access decisions, and specified the competencies the company needed, thereby aligning the new organization and roles to facilitate the achievement of the ultimate goal—providing patients with medicines they need at acceptable prices.

To us at Baxalta, “patient access” streamlines the value chain within our company to ensure our products meet our customers’ needs, and in the end create solutions that result in value for the patients, our company, and the healthcare system at large. While it was a significant challenge to arrive at an entirely new paradigm for our organization, the following steps were instrumental in achieving this shift that ultimately has made Baxalta a more focused organization.

1. Start with an outside-in perspective

Healthcare authorities do their best to respond to the increasing needs of an ageing and "empowered" patient population on the one hand and have limited resources in healthcare systems on the other. As such, they are often required to limit access within their respective markets to innovations they perceive as reducing costs or delivering superior value, or ideally both. While this is not a new challenge, it has become much more intense in recent years.

Baxalta realized that it must understand the value of a drug, especially of a new drug or treatment, from the perspective of those influencing the decision to provide access. This was the starting point of Baxalta’s journey to redefine market access:

» To define the key deliverables required.
» Look at the competencies needed to produce the deliverables.
» Define roles that are built around these competencies.

In the process, Baxalta broke with a few paradigms in the healthcare industry, and validated others. “The result is an innovative, customer-centric way of ensuring Baxalta staff is optimally positioned to understand patient needs and translate these into a value proposition that matters to payers,” explained John Glasspool, executive vice president and head of corporate strategy and customer operations, Baxalta.

2. Define the competencies needed tomorrow

Instead of focusing on the gaps visible today, Baxalta’s leadership team challenged the global organization to look forward and identify the competencies required to compete effectively in the future and to build a model that anticipates these

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<tr>
<th>Access Transition: Old Trends vs. New</th>
<th>Past</th>
<th>Future</th>
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<tbody>
<tr>
<td>1 Products introduced on their own therapeutic value</td>
<td></td>
<td>Need for evidence to substantiate comparative value and improved outcomes</td>
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<tr>
<td>2 Value defined as clinical efficacy and safety</td>
<td>Value extends beyond the product to healthcare solutions</td>
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<tr>
<td>3 Therapy choice dominated by physician</td>
<td>Economic stakeholders influencing choices</td>
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<tr>
<td>4 Healthcare delivery location determined by provider</td>
<td>Patient-centered healthcare</td>
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<tr>
<td>5 Policy-makers, regulators nationally focused</td>
<td>Policy-makers, regulators and patient groups are connected globally</td>
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<tr>
<td>6 Healthcare budgets adequate</td>
<td>Enormous pressure on budgets leading to increased tendering</td>
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needs. Interviewing a broad range of stakeholders inside the company helped to identify the trends shaping the market access landscape globally (see chart on facing page). Once identified, Baxalta validated these trends with industry experts.

3. Test the model with scenarios
Securing access to innovative medicines is a team sport. How does one organize operationally to address the needs of patients, payers, providers, policy-makers, and professionals? We defined specific scenarios—such as a health technology assessment (HTA) for a new product—to test whether the competencies were the right ones and think through how they would be deployed (see example in chart above).

Since the needs of payers and other access stakeholders at the local level differ, the scenarios helped test whether global, regional, and local roles were properly designed and the interfaces between them sufficiently clear; and highlighted the linkages with other functions critical to access such as R&D, marketing, and regulatory. Walking through the scenarios helped clarify how the competencies helped address the needs of the external stakeholders. As a result, the scenarios reduced the inevitable anxiety and confusion associated with reinventing a function such as “market access” and evolving the approach to “patient access.”

4. Prepare for a successful ‘launch’
We found that in order to ensure the new model is properly implemented, we would need to approach it as if we were launching a new product. Roles and responsibilities needed to be redefined, and training programs needed to be developed to help close the competency gaps. The roles have a much more global focus, so processes were implemented to define how global teams will collaborate.

We must understand the value of a drug from the perspective of those influencing the decision to provide access

Treating the launch of a new patient access organization like a product launch helped the Baxalta team involve key internal and external stakeholders from the start, allowing new ways of collaborating to better meet patient needs.

Think ahead
Basing the new patient access model on forward-looking competencies was a crucial step, uniquely enabling our access organization to succeed today and be ready for tomorrow’s likely challenges. Having external opinion leaders contribute to internal thinking strengthened and completed our efforts. The scenarios were critical in helping the organization think through how these competencies would be deployed.

They helped patient access professionals visualize collaboration with each other as well as the larger organization to ensure the outputs created meet the needs of the various stakeholders. Treating the launch of a new patient access organization like a product launch helped Baxalta make sure the company was prepared to embrace innovative ways of working to provide patients with the medicines they need at acceptable prices.
Tapping out-of-network sources can be a plus for brand campaigns

Today, disruptions in both healthcare and marketing have created new risks for pharma brand leaders when they consolidate their full suite of advertising services—from media/search engine marketing (SEM), social, and digital execution to insights and strategy, analytics, and digital agency of record (AOR)—with a single network, or worse, a single network agency. To minimize the risks, many brand leaders are embracing a new agency service model called “prosolidation” that adds independent agencies into the mix, breaking the decades-old trend of agency consolidation.

Consolidation vs. prosolidation
The watershed moment for agency consolidation came in 1994 when IBM consolidated $500 million in agency spending. It was the largest such shift in advertising history but, more importantly, it worked. IBM cut costs and revitalized its brands with a cohesive message and strategy. Other companies joined the trend, hunting for leverage and efficiencies through consolidation. In pharma, too, advertising dollars consolidated with a holding company and its network of agencies became the de facto “prescription” in the 1990s and 2000s—a basic calculation of maximizing a benefit-to-risk ratio.

But today, that calculus is changing. Higher risks have emerged in network relationships due to three recent industry forces: the rising cost of procurement, the maturation of digital, and the growing complexity of pharma products and their marketing needs. To mitigate the risks, pharma marketers are supplementing their network relationships with specialized talent, untethered innovation, and leading-edge capabilities from out-of-network sources. The new trend may not have a watershed moment to point to, as in 1994, but now it has a name: prosolidation.

Prosolidation is the new service model that adds independent agencies back on the roster in order to have them work in concert with network agencies. Not a return to the days of pre-consolidation, prosolidation instead optimizes the consolidation model by replacing the “cons” (risks) with “pros” (benefits). It empowers clients to build greater value around their brand by freeing them from complete dependence on a network for AOR solutions—whether for strategy, creative, digital, media, or social.

Consolidation Lookback: Benefits and risks
Consolidation was basically a financially driven idea. Its chief benefits were discounts, standardized rates, and streamlined contracts. Greater efficiencies for clients and agencies were realized by reducing the number of stakeholders, handoffs, overlaps, and other redundancies encountered with a multiple-agency model. Support services, such as finance or IT, could be centralized, as could multiple account teams. For clients, consolidation gave procurement more leverage in negotiating prices and terms, enabling companies to be more aggressive in increasingly competitive markets. For networks, consolidation enabled agencies to deliver global scale and more consistent execution. Brand experiences were made more potent and uniform by a single entity than by multiple agencies.

But the financial and executional benefits gained from network contracts came with risks, too. According to Bob Jansen, the founder of Zensights and member of Pharm Exec's Editorial Advisory Board, “In a world of consolidated holding companies, pharma manufacturers and their sourcing departments are doing everything possible to drive down cost—without a true understanding of how the deliverable that they are negotiating for their internal clients will ultimately look.” Brand leaders, on the other hand, have long understood and contended with the risks:

• **Junior staffing.** In order to compete at the price point negotiated in the winning contract, network agencies run the daily work on an account with junior staff, who cost less than their senior counterparts. To further save expenses, agencies often stretch their staffing too thin.

• **Conventional thinking.** With junior staffing, innovation and independent thinking, the very capital of the creative agency, can be lacking, or even missing. Real expertise born from deep experience is increasingly absent on network agency brand teams.

• **A culture of managers.** The sheer size of a network demands a culture of managers (who keep the machine running) versus
leaders (who innovate). It reinforces the status quo.

» **Homogenization.** In an attempt to be all things to all customers, networks often end up homogenizing their capabilities and service offering. The entire industry of networks has raced itself to the middle ground and, as a result, network agencies tend to deliver virtually indistinguishable products.

» **Reduced competition.** When such a large percentage of agencies are controlled by a small handful of people, there are fewer incentives for competition or innovation, and their offerings become mediocre and slow to keep pace with emerging media and other trends.

**New risks with consolidation**

Although pharma companies and agencies exist in a constant state of adaptation, there are three trends right now in particular that are making the risks of consolidation more serious and the benefits of prosolidation more favorable:

1. **The rising cost of procurement.** The financial benefits of consolidation are no longer what they used to be. Drew Sigafoos, director of strategic sourcing at Otsuka (US), asks, “Do pharma companies really get the financial benefit of networks when they have to build such large procurement or strategic sourcing groups?” At some of the largest companies, Sigafoos notes, commercial procurement teams have grown to more than 60 employees, and overall procurement groups to more than 300. The financial burden of running such large procurement groups ironically diminishes or even completely negates the discounts they negotiate with networks. Negotiating with an independent agency, on the other hand, is a shorter, more straightforward process.

2. **The rise of digital demands greater innovation and novel capabilities.** The evolution of digital media means that constant optimization is needed to maximize value from marketing efforts. The network model of creating a campaign and repurposing it across channels *ad nauseam* is outdated; advertisers lose out on valuable opportunities for innovation and content marketing. In general, marketing, technology, and healthcare are converging. Digital capabilities transform our ways of working, and today’s digital landscape needs independent agency partners who can keep pace.

3. **The complexity of drugs demands increasingly niche skills and nimble services.** As the medical field advances, pharma treatments are growing in specificity and complexity. The proliferation of disease subtypes based on biomarkers, new drug modalities, and their underlying science spell out new areas of expertise. Product promotions increasingly differ across audiences, and company pipelines show a shift to more targeted therapies in lieu of mass-market blockbuster drugs. Disruptive trends—such as wearables, digitally connected health services and devices, patient empowerment, and outcome-driven incentives—all signal a need for diverse specialized talent. The management of talent in a network agency is often subject to misallocation, whereas independent agencies are better able to assemble purpose-built teams with the expertise to understand the implications of these new developments and cater to each brand’s needs.

**The new prescription for pharma marketing**

Rhetorically, prosolidate is a clever word; conceptually, it’s an idea whose time has come. Prosolidation offers a new service model where pharma marketers can reap the benefits of independent agencies and network agencies—a considerable advantage over the preceding consolidation model.

Without an overhead organization, independent agencies maintain ownership of their own set of priorities, which translates into direct responsiveness to client needs. In comparison, network agencies are required to satisfy the priorities of their holding company first; they must respond to the pressures of the network contract and the need to “feed the machine” with volume.

As marketers look for ways to leave less money on the table, independent agencies have become critical to reducing the capability gaps and innovation blind spots created by consolidation...
HEALING LIVES. HEALING THE FUTURE.

We broke the ground for AbdiBio, the largest biotechnological pharmaceuticals manufacturing facility in Turkey.

To heal more lives, for a better future and a better world...

abdilibrahim.com
The 21st century has brought much change to Turkey. GDP tripled from under USD 267 billion in 2000 to over USD 822 billion in 2013. Massive infrastructure projects created over 13,000 km of roads, 24 new airports, 88 new universities, and 650 hospitals. For the healthcare and pharmaceutical industry, this period was defined by the Healthcare Transformation Program (HTP), which saw the complete overhaul and expansion of the Turkish Healthcare system between 2003 and 2013, with three separate social security agencies combined into a unified social security institution (SGK). During the same period the private sector was expanded and brought into the national reimbursement system, and more than 98 percent of Turkey’s population were brought under national insurance coverage.

Having reached the end of this transformational era, what will be the trends, dynamics, and initiatives that drive change in the Turkish pharmaceutical industry in the coming years?
THE END OF AN ERA

This transformation caused pharmaceutical sales volumes to skyrocket at a 9.6 percent CAGR between 2003 and 2013, according to the Turkish Drug and Medical Devices Agency (TITCK). The reimbursement rate increased to more than 95 percent, and patient access to healthcare services and general healthcare awareness improved each year. Of course, achieving this status quo came at a price, and after seeing healthcare expenditure begin to rise rapidly in the late 2000s, the government instituted aggressive public discounts in 2009 and 2011 to contain spending. As such, pharmaceutical expenditure grew by just three percent in real terms over the same period.

“At the time we took office in 2002, Turkey was not in a good position with regards to the economy, various social issues, and of course the state of the public health system,” explains the former minister of health Recep Akdağ, who led the transformation program. “The entire country was waiting and hoping for change, and the expectations for this change to happen were very high.

SELECTED KPI TARGETS FROM VISION 2023 ACTION PLAN

<table>
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<th>Innovation Capacity</th>
<th>2014</th>
<th>2023</th>
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<tbody>
<tr>
<td>Quality of Scientific Research Centers</td>
<td>89th</td>
<td>Top 30</td>
</tr>
<tr>
<td>Retaining Scientists and Engineers</td>
<td>35th</td>
<td>Top 20</td>
</tr>
<tr>
<td>Number of new local molecules</td>
<td>0</td>
<td>At least 1</td>
</tr>
<tr>
<td>Number of clinical trials conducted in a year (2013)</td>
<td>1,267</td>
<td>Approx 3600</td>
</tr>
<tr>
<td>Export/Import ratio</td>
<td>10%</td>
<td>107%</td>
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</tbody>
</table>

Compiled by Investment Support and Promotion Agency of Turkey.
This was both an advantage and disadvantage for us; we were able to gain strong political commitment and public support which were essential for reforms of the magnitude that were required... We were able to achieve real progress through our efforts, and together the changes that were made transformed the healthcare system in Turkey to the extent that it is now being used as a model for many developing countries.” Minister of Labor and Social Security Faruk Çelik states that the Healthcare Transformation program is “now used as an example of good practice in healthcare systems around the world,” and that due to the reforms Turkey has “a new social security system, which is more compatible with international standards, offers high quality services, covers the entire population, and is financially stronger than before.”

Since the transformation program’s reforms ended in 2013, and with it Akdağ’s ten year mandate as minister of health, the driving force for change and progress in the sector faded away. The need for a new vision for the sector arose, as well as the opportunity for the industry associations to play a role in developing the government’s new strategic plans, particularly in the pharmaceutical industry. Murat Barlas, chairman of Liba Laboratories and the senior board member of the Pharmaceutical Manufacturers Association of Turkey (IEIS), explains that “the current plan for the pharma sector until 2023 was prepared by the industry and delivered to the government.” This plan was published by the association in November 2011, in a report entitled ‘Partnering with the Government to Globalize the Turkish Pharmaceutical Industry,’ while the AIFD published a similar strategy document in 2012 titled ‘Turkey’s Pharmaceutical Sector Vision 2023 Report’, and the two garnered enough attention that several items from their action plan surfaced in the government’s own plans, including the national Tenth Development Plan.

“Going forward, we will be prioritizing R&D initiatives, including health studies and medical innovation,” details Akdağ’s successor, minister of health Mehmet Müezzinoglu. “It is for this purpose that we founded the ‘Department of Health Institutions of Turkey’, which will follow developments in medicine closely. The Ministry of Health is encouraging the production of
medical devices and medications in Turkey, and we will be supporting the development of vaccines, biosimilars, and other high value added medicines in Turkey.” Article 1.16 of the Tenth Development Plan outlines a ‘structural transformation program within the health industry,’ and includes the target for 60 percent of pharmaceutical products and 20 percent of medical devices consumed in Turkey to be produced domestically by 2018. Other targets for the healthcare and pharmaceutical industries have been set under the aegis of President Recep Tayyip Erdoğan’s ‘2023 Vision’, a set of goals for the country to achieve by the 100th anniversary of the Republic of Turkey’s foundation in 1923, which include aggressive targets for increasing exports and improving competitiveness for R&D investment.

While much progress is being made, questions remain regarding the feasibility of achieving these goals, and the effectiveness of the initiatives that have been introduced thus far. “The vision that the government has for the pharma sector will be achievable only if it changes its perspective on the industry as it stands,” argues Barlas. He explains that “today, for our government, the most important issue is the cost of healthcare and pharmaceuticals… if this perspective shifts and we are able to communicate our needs better to the government, then achieving this vision may yet be attainable.” Yet, much progress is being made across the industry with numerous biosimilar development projects underway, and other investments in higher value manufacturing activities taking place. In fact, while “some existing policies are still contradictory to this 2023 vision,” Pfizer country manager Elif Aral alleges that “the government has made it clear that they will support the industry moving forward, and not continue to treat it as a cost that must be contained.”

**METAMORPHOSIS UNDER PRESSURE**

In terms of Turkish Lira, pharmaceutical spending returned to above inflation growth in 2014, rising 10.1 percent to TRY 16.3 billion (USD 7.45 billion) in 2014, after actually falling 4.1 percent in 2012, according to IMS and TurkStat. However, local manufacturers are quick to point out that this growth is not distributed evenly across the industry. Cengiz Celayir, president of the Pharmaceutical Industry Association of Turkey (TISD), points out that “original imported products make up only three percent of the market by volume, but have a market share of 27 percent in terms of value, and this is the segment that is seeing some revenue growth at present.”

Santa Farma chairman and CEO Erol Kiresepi argues “this is the problem faced by the local industry today. Our prices are low, and the products we’re offering on the market are primarily generics…the market increase last year has primarily been a result of high value, low volume products coming from multinationals.” In line with the government’s heavy emphasis on R&D and producing more value added pharmaceutical products, Kiresepi asserts that “companies need to focus on building up exports, reinforcing R&D, and restructuring portfolios to account for changing market dynamics. As such, he contends “the future of local producers will lie in specialty products, OTC, and exports, all of which we’re currently building up our capabilities in.”
“The pricing situation is now a fact of life,” says Cem Baydar, senior principal consultant for IMS in the Turkey and Near East region. Reference prices in Turkey are constructed from the lowest price in France, Greece, Italy, Spain or Portugal, converted to Turkish Lira at a rate of TRY 1.9595 per EUR, and then the public payer, the SGK, pays a discounted price, which was set in agreement with the industry consensus in 2009 at 11 percent. In December 2009 the government arbitrarily raised the discount rate to 23 percent, then to 31.5 percent in December 2010, and again to 41 percent in November 2011; the conversion rate was not changed at all until June 2015, when it was raised by 2.07 percent to TRY 2.00 per EUR, and in July it was increased by another 3.9 percent to TRY 2.0787 per EUR, at which point the market exchange rate was approximately TRY 3 per EUR. As a result, Turkish pharmaceutical prices are now at approximately 38 percent of the lowest prices in Europe, save in a few special circumstances where alternative pricing arrangements are in place.

Ümit Yaldız, head of Greater Turkey for Merck Millipore, argues that “with the change in the pricing model... companies were forced to restructure their businesses and overhaul their operating models; as such, the industry has become much more efficient, and much more competitive in the global arena, and from this perspective cutting prices was the right move and the policies have had a positive impact.” Cem Baydar of IMS explains that “companies had to adapt and implemented change management programs that are now mostly completed,” detailing how the top ten companies have reduced their sales forces by 44 percent over the last five years.

On the topic of spending growth, Baydar says that “the market has changed and is going in a new direction... specialty care is on the rise... and the hospital channel is outpacing the retail channel; sales in the hospital channel increased by 20 percent last year, while retail only increased by 8 percent,” and will continue to grow with the “growth of private hospital chains and the opening of new public hospitals.”

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### OVER THE LAST FIVE YEARS, VOLUME HAS BEEN THE BIGGEST GROWTH DRIVER IN THE TURKISH MARKET

#### SOURCE OF GROWTH ANALYSIS, NET GROWTH - VALUE, Mn USD

<table>
<thead>
<tr>
<th>TOTAL GROWTH</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tr>
<td>167.4</td>
<td>-261</td>
<td>400.95</td>
<td>670.5</td>
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- 800.55
- 330.75
- 306.65
- 153.9
- 797.4
- 716.85
- 459.65
- 36.45
- 1.35
- 68.4
- 36.45
- 60.75
- 34

- New Pack
- New Brand
- Price Effect
- Volume Effect
- Withdrawn
- Total Growth

Source: IMS Dataview Retail Hospital Database, December 2014.
Growth is calculated vs previous year.
The healthcare system itself is growing rapidly, including the private hospital sector, which is tied closely to the public system. “70 percent of patients in private hospitals are referred from the public system and are covered [at least partially] by social security,” explains Cevat Sengül, secretary general of the Association of Private Hospitals and Health Institutions (OHSAD). “18.9 percent of Turkish hospital beds and 23.8 percent of specialist physicians are in private institutions,” according to Sengül, yet private hospitals “have 38.3 percent of the ICU beds and perform 53 percent of class A1 surgeries, the most complex category of procedures.” Furthermore, the private sector is expected to grow significantly: Sengül expects “that by 2020, the sector’s share of private hospital beds will rise to 53 percent from 42 percent today.”

For the pharmaceutical industry, this means that the private hospital system represents a large and fast growing market. Ufuk Kumrulu, chairman of IV solutions manufacturer Polifarma, explains that “the private healthcare sector has been growing strongly since the early 2000s, and Polifarma identified this trend early on, so we have sold and marketed to private hospitals for many years now.” According to Kumrulu, “today 30 percent of the total [parenteral solution] product consumption is in the private system, and we think the private sector’s share of the market will continue to grow over the next several years.”

The public sector also continues to grow, with new hospitals being opened across the country and occupancy rates rising. “In public hospitals, the system is based on tenders,” explains Kumrulu, and this tender process began to change in the last year, “as in all cities’ hospital management systems, purchasing, and stock management have been consolidated underneath a single institution, which has raised the size of tenders and depressed prices.”

While it is critical that Turkey invests in expanding its healthcare system to ensure that infrastructure is able to support the growing demand for healthcare services as Turkey’s population ages, the country must also invest in physicians to get the best value out of those investments. “The current defining circumstance in Turkey is that we have limited human resources in healthcare and have the lowest number of doctors per capita in Europe,” explains former minister of health Akdağ. UCB’s managing director, Özdemir Şengören, indicates that this shortage creates significant access problems for patients. “When you drill down,” she says, “you discover that in Turkey there are patients who have had an epilepsy diagnosis for many years… who still complain that they can’t find … an epileptologist, to treat them. Patients also complain that when visiting hospitals, they can’t ask their physicians the questions they have because each patient has very limited time with the doctor,” due to the incredible number of patients each physician must see each day.

Murat Uslu, general manager for Actelion Turkey, echoes Şengören’s comments. “The Turkish healthcare system has a lot of excellent facilities, while some others have quite a way to go in terms of equipment and workload, and this of course affects physicians’ ability to efficiently diagnose patients. The number of physicians, and the number of specialists per capita is very low in Turkey, making it difficult for physicians to dedicate sufficient time to each patient.”
WHY INVEST IN TURKEY?

"Turkey is already an attractive investment destination for multinational pharma companies for a variety of reasons, including geographic location, market size and composition, the aging population of 75 million people and likely healthcare spending escalation in the future," explains Ümit Dereli, secretary general of the AIFD. "More importantly, the timing is right as Turkey is still in a phase of fast economic growth relative to developed economies. The timing will not remain this favorable for long, and there are a number of factors that are discouraging investment in the industry, from Turkey or abroad, at present."

Dilek Bayraktar, secretary general of the innovative medical devices industry association (ARTED), adds that "the average Turkish person is still getting used to having access to publicly reimbursed healthcare services, so healthcare demand will certainly rise on both a per capita and aggregate basis. Economic growth is also expected to continue at a rate above that of the developed economies... and Turkey continues to be the most stable country in the region. On the whole, investing in Turkey makes sense; the remaining challenges are making it attractive for medical device manufacturers specifically." This situation is the same for the pharmaceutical industry, with Novartis country president Peter Catalino saying that despite the attractive economic factors, Novartis "would need to see much stronger investment incentives that were more competitive with those offered in other countries," before considering large scale investments in Turkey.

In fact, some companies have recently chosen to invest in Turkey on these macroeconomic factors alone, despite the lack of competitive pharmaceutical investment incentives. Recordati recently made the decision to develop a second production plant in Turkey, with a planned investment of USD 50 million. "Turkey's entrepreneurship friendly environment is one of the two main reasons why it is the right time for Recordati to invest here," explains İsmail Yormaz, VP and regional director for Recordati's southeast region. "The other reason is the demand, the need that currently exists in Turkey and will grow in the coming years." He continues, saying "I do not know what will happen in the short term for the Turkish pharmaceutical environment, but I am quite certain of what will happen in the mid to long-term; the Turkish pharmaceutical market will continue to grow, because Turkey has a growing population, one of the youngest populations in Europe, and as this population ages its medical needs will increase, particularly in chronic areas. For the last 12 months Turkish pharmaceutical consumption has grown in the double digits. Furthermore, Turkey has strong human resources for pharmaceutical production with a lot of expertise, experience, and knowhow. Lastly, the surrounding region also has growing needs for medication, and given the political situation in some nearby countries, Turkey is optimally positioned to supply these markets."

Feliz Balcay, general manager for Chiesi Turkey, echoes Yormaz, explaining that...
Chiesi’s “aspiration is to position Turkey as a hub for management and manufacturing; Turkey is already positioned as a regional management center for many multinational pharmaceutical companies. However, there is still a need for a better framework for potential investors in manufacturing in the country.” These multinationals include GSK, who relocated their regional management hub for their pharma business for the Middle East, North Africa and CIS regions to Istanbul in 2012. Other companies have since followed. Ilker Özbay, general manager for Daiichi Sankyo Turkey, explains that “since 2012, we have expanded our business to cover markets such as Azerbaijan, Kazakhstan, Algeria, and soon Ukraine and Nigeria… We prioritized this geographic expansion in 2012 because it was apparent that the Turkish market was unlikely to grow… [and this strategy] helped us achieve revenue growth in a stagnant market, and increase our profitability.”

Thus far, the Turkish government has not introduced any meaningful incentives to encourage such investments, but due to the current market access situation in Turkey, there are certain advantages to developing local production. Products manufactured in Turkey are given significant advantages at the reimbursement stage, strongly demonstrating the government’s aim to achieve a local production rate of 60 percent by 2023. Yadigar Gökalp İlhan, president of the Social Security Institution (SGK), explains that the institution encourages “companies to produce medications in Turkey instead of importing by providing an easier payment system… With respect to incentivizing local manufacturing, some arrangements were made for adding locally produced products to the SGK’s reimbursement list, and these products will have the privilege of getting reimbursement first.”

The standard of pharmaceutical reimbursement is quite high, as Novo Nordisk Turkey’s general manager Şebnem Ayşar Tuna affirms. “Turkish universal health insurance provides a very strong foundation for healthcare treatment in general; … we are able to provide modern insulins for the treatment of people with diabetes; established insulin products are fully reimbursed.” Yet, for highly innovative products, “market access is the main barrier of growth for innovators, to the extent that one of our combination products was submitted for reimbursement 960 days ago and still hasn’t been approved,” says Ilker Özbay, general manager of Daiichi Sankyo Turkey. Under this incentive structure, of strong reimbursement but sometimes slow and limited market access, the Turkish Pharmacists Association (TEB) has become the country’s largest importer of registered and unregistered drugs from abroad. However, in hope of creating a more favorable appeal for foreign companies operating...
Nobel: The Global Turkish Brand

Nobel is Turkey’s most internationalized pharmaceutical producer, having begun the process of developing international operations in the early 2000s, when they “established subsidiaries outside of Turkey, and then built two foreign production facilities in Uzbekistan and Kazakhstan,” according to the company’s chairman, Hasan Ulusoy. “In 15 years, we have established offices with our own marketing teams in 24 countries, and our products are marketed and sold in nearly 50 countries in total,” he explains, pointing out that in 2014 “our turnover outside of Turkey reached a value of USD 120 million, while our export volume from Turkey grew to USD 60 million, which represents more than 1/14th of all Turkish pharmaceutical exports.”

More than just establishing a strong international presence, Nobel is the only Turkish company to have established a pharmaceutical brand on a global scale. The firm’s Tylo Hot brand “has become one of our flagship products, which we are marketing in 20 different countries under the Tylo Hot brand, and this makes it the only Turkish pharmaceutical brand with significant international recognition at present.”

Regarding the future, Ulusoy hopes “that the company can continue to expand in an international way, and become a truly global company. Competition abroad is tough, but so is it in Turkey, and we have developed excellent quality standards and a large, strong portfolio over the years, so we are well prepared to compete with international and local companies in other markets.”

in Turkey, the government has begun implementing new channels that will allow these companies to play a more active role in addressing the clinical needs of Turkish citizens. “Recently, SGK commenced an initiative to involve more Turkish affiliates of multinational pharmaceutical companies [to import],” says Gökhan Gökçe, one of YukselKarkınKüçük’s founding partners. “Currently, although more so in the past, trading companies have been supplying products to TEB, after which point TEB would sell to SGK. Now, the subsidiaries of those large manufacturers in Turkey will be the ones interacting with SGK and adopting alternative reimbursement models.” Such an initiative will help create a shared platform for foreign companies to expand their current commercial activities in Turkey through imports, while also expanding the range of medicinal treatments available for the local population and alleviating any supply shortages for certain medications.

Under the leadership of Nezih Barut, the third generation of the family to run the company, Abdi Ibrahim has sought to become and be seen as increasingly innovative, and as such, the company embarked on a 50-50 joint venture with leading Japanese innovator Otsuka in 2012. Tuna Yavuz, general manager of the joint venture, called Abdi Ibrahim Otsuka, argues that this strong “reimbursement system poses other challenges, as reimbursement payments are currently made according to the product class, meaning that the social security institution will buy and pay for illegal generic copies of patented drugs; the responsibility of enforcing a patent falls on the patent holder, who must sue the patent violator, resulting in costly and extended legal battles.”

GMP requirements and inspection timelines also indirectly encourage local production. Daniel Lucas, managing director of Lilly Turkey, explains “that since 2009, a Turkish GMP certificate is required prior to an application for marketing approval, which requires an onsite inspection and thus has significantly delayed the registration process.” Yavuz claims that “to expedite product approvals, we decided to establish local production of our products using Abdi Ibrahim’s facilities; this accelerated the GMP certification process significantly.”

Many other firms have and are utilizing the option to localize production through toll-manufacturing agreements with local manufacturers. “Lundbeck is very proud to have taken action, and has transferred technology and brought innovative manufacturing activities to Turkey,” affirms Şebnem Girgin, the managing director of the company’s Turkish affiliate. “With our local manufacturing partner, Pharmavision, we have completed the technology transfer necessary to produce our innovative antidepressant product and we obtained marketing authorization for this molecule as a locally manufactured product at the end of 2014.” According to UCB Turkey’s managing director Özdemir Şenören, “93 percent of our sales by volume are produced in Turkey, mostly in our established brands. This is very critical for a small company like UCB, and for our size we have made some very effective investments in partnerships with Pharmavision, Bilim, and Adeka. In terms of 2023 objectives, we have efficiently
International Turkish brand in pharma

Since 1964, Nobel İlaç’s high quality products have been at the service of human health in over 50 countries on three continents through its 20 international subsidiaries.

Nobel, the pharma group, open to Turkey, to the world, to novelties and partnerships.
localized production and helped to increase the Turkish manufacturing capacity utilization rate.”

However, it is important to recognize that Turkey does recognize foreign GMP certificates in theory, if there is mutual recognition of Turkish GMP certificates in the country in question. At present, Turkish GMP standards are not widely recognized, and this is limiting the export potential of the Turkish industry, for both Turkish producers and multinationals considering investing in the country. According to Özkan Ünal, president of the Turkish Drug and Medical Devices Agency (TITCK), this situation is in the process of being resolved. “Turkey applied to become a full member of PIC/S in 2013… At present, we are aiming to become a full member of PIC/S in one year.” The expectation is that as a fully accredited PIC/S member, Turkey will be able to establish mutual recognition agreements with other members more easily, and in Ünal’s words, “once this accreditation comes...
through it will bring many new opportunities to our pharmaceutical manufacturers in export markets.”

**QUALITY AND CAPACITY**

With 78 pharmaceutical manufacturing plants registered in Turkey in 2013, owned by 74 separate companies, 16 of them multinationals, the number is continuing to grow with investments in greenfield facilities from both Turkish and multinational players continuing.

Yet, according to Cengiz Celayir, president of the Pharmaceutical Industry Association of Turkey (TISD), “roughly 30 percent of conventional dosage form manufacturing capacity is idle.” Thus, “we have the capacity to export... and there are many opportunities for growth.”

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**TOP 15 LEADING CORPORATIONS* SALES GROWTH BY VALUE**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>2014 Sales (MN USD)</th>
<th>'13 - '14 Value Growth</th>
<th>Compounded Annual Sales Growth Rate '10 - '14</th>
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<tr>
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<td>NOVARTIS</td>
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<td>3.5%</td>
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<td>ABBOTT</td>
<td>129.6</td>
<td>20.2%</td>
<td>7.1%</td>
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*Novartis includes Sandoz and Alcon; Sanofi includes Zentiva, Genzyme and Sanofi Pasteur.

Source: IMS Dataview Retail Hospital Database, December 2014.
companies that do some contract manufacturing on the side,” which has in effect prevented the establishment of pure contract manufacturing organizations in Turkey, apart from a single example, Pharma- vision. As Murat Barlas, chairman of Liba recounts, this is not a new situation. “It started in the 1990s... at that time we re-
alized that there is a huge unfilled capacity in Turkey. In competitive areas, there were so many similar products that most of them
did not bring any added value, and instead, many pharmaceutical products were becoming more like commodities.”

The distribution of this excess capacity is far from uniform. Menarini’s Turkish subsidiary, Ibrahim Etem Menarini, “would like to be a source for Menarini affiliate in the region,” according to managing director Uğur Bingöl, but “due to our very high utilization rate of our facilities we do not have the capacity to become a true manufacturing hub.” Currently the affiliate “exports a small number of products to countries like Azerbaijan, Afghanistan, Kosovo and Somalia.” Bingöl continues, saying “having a very high level of utilization, one of the highest in Turkey, also means that we are

One of the most sophisticated and technically advanced manufacturers in Turkey, Deva, shows that demand for manufacturing

The low pharmaceutical pricing environment and demand for cost effective con-
tract manufacturing services in Turkey has clearly influenced the design and vision
behind the newest Turkish pharmaceutical manufacturer, Pharmactive. With a new fa-
cility with a capacity of 330 million units per year, built at a cost of USD 200 million, the company’s first concern was “minimizing production costs to have a competitive edge,” according to president Haluk Sancak. “It is a burden now but in time it will

Sancak contends that Pharmactive can bring unique value to clients as a contract manufacturer, “since our operations are still expanding and being developed, the course of this
development can be influenced or molded by a third party.” He continues, saying Pharmactive is “happy to accept the guidance, advice, and support of global pharmaceutical players who would like us to develop specific capabilities and tech-

In this regard, Pharmactive is a production platform for the global pharmaceutical business that can be adapted to fit their spec-
ic needs.”
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capacity of 70 million units in various dosage forms that produce a range of solids, liquids, softgelatin capsules, semiliquids, sterile eye drops, and antiasthmatic inhalers,” explains Tagiyev, and “despite the fact that World Medicine has strong sales in the countries that we export to, because our Turkish production facility is quite new we still have excess capacity to support our expansion.” Pharmactive’s facility is significantly larger, “with a production capacity of 330 million units per year, of which we are utilizing approximately 15 percent at present, and hope to increase this to 18 to 20 percent by the end of the year if things go well,” general manager Köksal Ülgen details. Erol Kiresepti, chairman and CEO of Santa Farma, also introduces his firm’s new facility, saying that the new plant will be located in an 80,000 sq meter area outside of the city, with a closed area of 42,000 sq meters... [and upon completion] “it will have a capacity of 150 million units per year. This is, by definition, the newest and most modern facility in Turkey.”

In addition to facilitating trade with the CIS and MENA regions, this new asset was meticulously designed in such a way to allow the company to eventually penetrate a developed market where many Turkish brands have dreamed of going, but few have actually gone—the United States. “We’ve been working with two international advisors to design the production facility in compliance with the anticipated changes to the FDA and EU GMP changes coming in the next few years,” highlights Kiresep. Ultimately, the aim of “this new plant will be to attract business not only from Turkish companies operating in the local market, but also international companies looking for superior and cost-effective manufacturing capabilities combined. However, Muzzaffer Bal, general manager of Ali Raif, highlights the importance of current export developments explaining that “until only a few decades [earlier], Turkey paled in comparison to other emerging countries with regards to export volume...
The economy was still in its early onset of globalization and exhibited more closed-border commerce—and the pharmaceutical industry was no exception.

The effects of globalization on Turkey's economy have been self-evident—increased trade activity, and in turn GDP, multicultural exchange of skills and labor, and an accelerated rate of industrialization. But, perhaps less obvious, are the effects on local Turkish pharmaceutical players and their strategies to drive commercial success. “Traditionally it’s been 50% in-licensing and 50% proprietary production. But as the local environment became increasingly accessible, with less stringent import controls and more favorable incentives for FDI, many of our former licensors either acquired their own Turkish distributors or established an affiliate office in Turkey,” recounts Bal. Founding partner of Yüksel KarkınKüçük, Gökhan Gökçe agrees. “In the interest of profitability, efficiency, and long-term sustainability, many of these pharmaceutical and medical device companies are [now] contemplating going direct to market,” leaving domestic pharmaceutical players such as Ali Raif to shift from primarily licensors to proprietary manufacturers—strictly to maintain a competitive positioning in the market.

“We had the opportunity to work with upwards of 20 MNCs at one point—enabling us to obtain several market leading positions across Europe over the years. Now we’ve extensively pursued our own R&D and production initiatives—producing approximately 75 percent of our own generics, with the remaining portion of our portfolio attributed to in-licensing,” details Bal. with the geostrategic advantages of Turkey based operations.”

MOVING UP THE VALUE CHAIN

With the Tenth Development Plan specifically aiming to encourage the production of medicines with “high value added,” Turkey’s government is seeking to create production of several categories of products, including vaccines, blood products, and biosimilars in Turkey. In pursuit of this goal, a few subsidy programs and public private partnership projects have emerged, and several multinationals have made significant investments to support the achievement of this goal.

Partnerships between Turkish pharmaceutical producers and multinationals are also on the rise under a variety of structures, but general manager Tuna Yavuz explains that Abdi Ibrahim Otsuka will be the only joint venture offering “the opportunity to manufacture several products within Otsuka’s portfolio of highly demanded, blockbuster drugs such as Samsca, Pletal, and Abilify, which brings high ‘value added’ activities to Turkey, and will help to build pharmaceutical exports.”

On the vaccine front, Pfizer has taken the lead. As Elif Aral, country manager for Pfizer Turkey explains, “in the last five years we developed a new, much more advanced facility to manufacture Prevnar, a vaccine that won the US Prix Galien in 2011. The new Prevnar manufacturing facility, developed in partnership with Mefar, is only the third manufacturing site for Prevenar in the world after sites
Atabay: Excerpt from Interview with Bulent Atabay

Atabay’s president, Bulent Atabay, discusses his company’s dedication to producing high-quality life-saving primary care products at accessible prices.

What is the most important decision you have made on behalf of Atabay?
The most important decision we ever made at Atabay was in defining the mentality of our business and the types of products we seek to develop. Our goal is to produce and sell high-quality pharmaceutical products at a reasonable price, and to select products that have a substantial impact on global public health. For us, paracetamol is the best example, as this is a cheap product that can save the lives of patients, and it can still be considered best in class.

How is Turkey positioned to be a competitive API producer?
Today, chemistry-related industries are slowly disappearing in the US and Ireland, and is the first locally manufactured vaccine in Turkey, with the first commercial batches completed in 2012.

As for biotech and biosimilars, Genzyme Turkey’s general manager Cenk Sokmen explains that “at the moment, Turkey does not have the necessary infrastructure for biotech manufacturing, however, looking at the president’s ‘Vision 2023’ strategies and relevant development plans it is clear that there is certainly the political will, the technical knowhow, and overall capability to accelerate our industry to the top ten.” The government entities directly engaged in biotech and biosimilar development projects include the Scientific and Technological Research Council of Turkey (Tubitak) and several ministries. Ersin Erfa, CEO of Centurion, says “the government has been very supportive of companies developing biotech manufacturing, providing some financial support and cooperating in the regulatory environment. Of course there are other countries with more robust incentive programs, but overall Turkey has offered an effective set of incentives, and clarity as to their policy agenda to minimize uncertainty, which is much more than we could have said a few years ago. As a Turkish company that wants to invest in Turkey, they’ve done more than enough to encourage us to do so.” Furthermore, the Turkish Drug and Medical Device Agency (TITCK) “is supporting the development of the Turkish biosimilar sector by developing an appropriate regulatory access approach that will allow biosimilar products to be evaluated more quickly and effectively,” according to the agency’s president, Özkan Ünal.

“Another program was created with the purpose of providing financial support to promising biotech projects,” explains Hasan Ulusoy, chairman of Nobel, “and after a competition in which 23 companies submitted 28 projects, Nobel’s submission was selected as the only project worthy of this support.” As of June 2015, a second project was approved under this program, submitted by Atabay. “We signed the agreement and have already started work on the development of an oncological biosimilar product from scratch, with Tubitak as a partner.” Ulusoy’s goal is to “bring the product to market by 2023, which means beginning phase II trials by 2019.”

For Atabay, assistant vice president Zeynep Atabay explains that “for this project we will be working with Marmara University, Boğaziçi University, and Istanbul Technical University and their molecular biology and biotechnology research center, Mobgam. 50 percent of our R&D expenses will be reimbursed… through Tubitak, who is also a partner for this project, and overall the expected timeline is 48 months, but we will be eligible for government support for an additional 12 months, which we will likely need.”

On the production side, several companies are already developing biosimilar manufacturing facilities, to be used for manufacturing products in conjunction with foreign partners.
HEALTH FROM THE PAST INTO THE FUTURE WITH CHEMISTRY AND BIOTECHNOLOGY

Atabay Pharmaceutical Fine Chemicals Inc. was started by organic chemist Bülent Atabay in 1970 at Atabay Gebze plant.

Since then, many pharmaceutical fine chemicals like ampicillin, amoxicillin, ibuprofen, trimethoprim, sulfamethoxazole, ethambutol, rifampicine and most important Paracetamol (Acetaminophen) were produced by Atabay Fine Chemicals Inc.

For Paracetamol (Acetaminophen) precursor paraaminophenol, Atabay has developed a very clean process using hydrogen gas and platinum catalyst to reduce nitrobenzene to paraaminophenol (Bamberger reaction). Then Paraaminophenol is acetylated to Paracetamol (Acetaminophen) using acetic anhydride.

Atabay's Paracetamol (Acetaminophen) plant is FDA approved since 1986. Atabay is the sole manufacturer of Paracetamol (Acetaminophen) in Europe. Atabay has been exporting Paracetamol (Acetaminophen) to Europe and America in the last thirty years.

In the recent years Atabay has been developing APIs for antiviral, antithrombotic and gastrointestinal finished dosage forms.
In Turkey, one pharmaceutical company has led the way in terms of talent recruitment and retention through their excellent workplace culture, winning an assortment of ‘Great Place to Work’ and ‘Respect for Human Life’ awards over the last five years: Daiichi Sankyo Turkey. Daiichi Sankyo was ranked the seventh best place to work in Turkey in May 2015, the highest ranking achieved by a pharmaceutical company, and in 2010 the company was selected as the best employer in the entire country. General manager Ilker Özbay believes that the company’s open communication policy lies at the heart of their great workplace culture, explaining that “when employees want to reach me I am always available whatever the time. We communicate positive and negative things in the same manner, honestly and respectfully,” and “our people are respected as humans as well as employees, as mothers and fathers who have family lives, and we try to always see things and make decisions from this frame of reference.” The time and resources invested in maintaining this company culture has benefited the business’ bottom line. It has also made them one of the most desired employers in the country. Özbay sees these awards as key indicators of the “emphasis that we place on the human aspect of business, and the value that we place in relationships,” which is of key importance for a firm that competes against industry giants such as AstraZeneca and Pfizer in cardiology, with just 35 sales representatives for the entire country. As he explains, “our strategy relies upon the quality of relationships, as our small teams must create strong effects with stakeholders to compete with larger companies that can visit them more frequently, and cover more prescribers”; to do this, Daiichi Sankyo has “made the choice to only focus on high potential regions and prescribers, maximizing the impact we can achieve with limited resources.” Such a strategy can work very well when implemented as Daiichi Sankyo Turkey has, allowing this small affiliate to match the level of sales achieved by a competitor with a sales force more than four times larger.

Erfa explains that Centurion, currently the market leader in many plasma derivative categories, is now “working with a strong and reliable partner, Amega Biotech from Argentina, to develop a new biotechnology manufacturing plant.” This facility “will produce, fill, and finish injectable biosimilar products, and we hope that its development will be finished in about 30 months.”

Abdi Ibrahim, the leading Turkish pharma company by revenue, began construction of AbdiBio, a greenfield biotech manufacturing and R&D facility with a planned cost of USD 100 million, in June 2015. “The facility will likely also perform a toll manufacturing function for some clients at the fill and finish stage.” He continues by saying that the primary goal is “to be able to work with biotechnology companies from all over the world to codevelop new biologicals, and to carry out the full production process.”

**THE INDUSTRY’S CRITIQUE**

Despite the progress the Turkish pharmaceutical industry is making in terms of producing higher value products, developing biosimilar production, and the exciting advancements in R&D, there are still clearly many issues to be solved in Turkey. The government is taking effective steps to support the industry in achieving many of its targets, but they have done little so far to improve other aspects of the environment for investment and innovation, particularly with respect to pricing. Of course, the industry recognizes that the government introduced mandatory public discounts for good reasons, as Feliz Balcay, general manager of Chiesi Turkey, explains. “The expansion of healthcare services [under the healthcare transformation program] had an impact on total healthcare expenditures; pharma spending soared and austerity measures were introduced to manage the total pharma budget.”

Containing spending has become particularly important in the context of healthcare sustainability, due to Turkey’s aging demographic structure. BMS Turkey general manager Ahu Yazici claims that “the system has spread itself very thin by trying to invest in all areas of healthcare, and therefore is not able to invest meaningfully in any area. Ideally, all healthcare costs must be controlled and balanced, including hospital costs, treatment costs, and other categories, with drug costs as only one component.” Balcay agrees that the Turkish “healthcare system is in need of better budget allocation in order to sustain their services. Innovative medicines and solutions should be assessed using a value-based pricing approach, as well as based on clinical outcome and safety.”
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While the industry does see some progress on reforming pricing practices, there are still doubts as to the government’s true intentions. Yazici explains that “we are also seeing the possibility of change for the pricing of certain product types, as the SGK is now discussing [various] alternative reimbursement models with the industry and other government stakeholders.” Pfizer Turkey’s GM Elif Aral clarifies: “they invited the industry to develop proposals for alternative payment systems, and while there are no concrete examples yet, discussions are moving forward.” While some are quite hopeful that these discussions may represent progress, and that these ‘alternative models’ could be designed to include value-driven pricing mechanisms, others such as Raf Vrints, Celgene Turkey’s general manager, maintain that “it is very important that we ensure these discussions do not become another cost containment exercise, and this may be difficult because we have seen this is still the SGK’s mentality.”

Ejder Kimya: Turning Towards Europe

Although pricing constraints have placed downward pressure on all players across the pharmaceutical value chain, API and raw materials supplier Ejder Kimya has managed to find opportunity in the face of this challenge. “Our success so far has been a function of the industry’s emphasis on quality,” argues the supplier’s managing director, Pervin Ejder. “That’s mainly because sourcing cheap raw materials with poor quality often leads to a higher total cost of ownership.” The Turkish supplier has not only managed to capitalize on this industry-wide mindset domestically, but also abroad, with foreign markets now accounting for roughly 50% of their business. “We’ve been exporting to countries such as Iran, Lebanon, Algeria, UAE. Now, we’re really focused on selling our laboratory services to European countries including Italy and Spain.”

Ejder Kimya’s overarching emphasis on quality service and competitive pricing has allowed the supplier to develop long-term partnerships with several multinational companies, including Kerry and Ajinomoto. But, perhaps in line with industry trends, Ejder Kimya has striven to go beyond the status of a simple supplier, and offer more value-added services covering their clients’ entire supply lifecycle. “For instance, three years ago, we partnered with MNC to establish a microbiology lab, intended for developing our competencies within food supplements. Last year, we bought out our partner’s shares, and have since used the facility to supply test services for the global cosmetic industry,” says Pervin.

Making progress on any of these points may be difficult due to various communication challenges, and a lack of clarity surrounding who in government should take the lead on various issues. İncesu notes that “it is very important to work closely with the key decision makers, to build real and strong partnerships with stakeholders, as well as to maximize the level of investment for our patients... We are in constant contact with not only the ministry of health, but also the ministry of labor and social security, the ministry of development, ministry of industry, the treasury, and many other government stakeholders. The challenge is addressing the right need to bring all parties together and create a valuable program for our patients.” For Şebnem Avşar Tuna, general manager of Novo Nordisk Turkey, “my most important responsibility is to continue to communicate with regulators and public servants... and to help find solutions that allow us to bring innovative products to patients in Turkey, while achieving a sustainable financial outcome.”

Ultimately, the Turkish government and its relevant stakeholders strive to keep its citizens’ best interests in mind when reforming existing regulations and introducing new policies.
“The Turkish life sciences industry is not so different from other developing countries’ markets,” says Sevi Firat, founding partner of Firat Izgi. “The Turkish government has made R&D in pharmaceuticals a priority and we see this as a way to break from the past difficulties the pharmaceutical market faced here. This is an area which generates jobs and income, while showing that Turkey is strong in terms of R&D globally and [that it] will become a rising star in its region.”

FRAMEWORK FOR R&D INVESTMENT

Multinational R&D investment in Turkey, particularly investment in clinical trials, has been quite limited relative to the size of the Turkish pharmaceutical market. Turkish R&D spending totaled TRY 14.8 billion (USD 7.77 billion) in 2013, just 0.95 percent of GDP according to TurkStat; President Erdogan’s ‘Vision 2023’ includes the target to increase this ratio to three percent of GDP by 2023. R&D spending on all healthcare related topics has grown at a CAGR of 8.3 percent per year since 2009, reaching TRY 2.217 billion (USD 1.16 billion) in 2013, with pharmaceutical investment on pharmaceutical clinical trials accounting for only TRY 85 million (USD 45 million).

One of the major limiting factors for pharmaceutical R&D investment in Turkey is the small number of certified clinical trial research centers capable of carrying out early phase trials; in a country of 75 million, there are only six such centers, with one of which only opened in May 2015. As such, Turkey is not particularly competitive in R&D when compared to countries with robust, often government funded, research infrastructure, and as such the ratio of pharmaceutical R&D spending to pharmaceutical expenditures in Turkey is low relative to many other countries. According to AIFD chairman and GSK VP and Area GM Emin Fadıllıog ˘lu, “our level of investment in R&D is USD one billion lower than it would be if our R&D share matched our share of [global] expenditures.” At present, the Tenth Development Plan includes targets to increase the number of clinical trial centers to 13 by 2018, and “to increase the number of clinical trials by 25 percent each year until

Recordati, established in 1926, is an international pharmaceutical group, with a total staff of over 4,000, dedicated to the research, development, manufacturing and marketing of innovative pharmaceuticals in many therapeutic areas, including a specialized line dedicated to treatments for rare diseases, that improve quality of life and help people to enjoy longer, healthier and more productive lives. Recordati has operations in the main European countries, in Russia, in other Central and Eastern European countries, in Turkey, in North Africa and in the United States of America. Recordati is present in Turkey since 2008 and today Recordati İlaç is the group’s fourth largest subsidiary.
2023,” according to TITCK president Özkan Unal.

Lundbeck Turkey general manager Sebnem Girgin indicates that the company has “been extremely satisfied with the quality of the neurology and psychiatry centers in Turkey when it comes to R&D cooperation, and we have identified a few as key centers for future global studies in this area,” demonstrating that expertise and capabilities do exist to support more investment in clinical trials. Founded in 1997, the key player in the Turkish clinical trial industry is Omega CRO, the first Turkish CRO, and according to CEO Berk Özdemir, “the only truly full service CRO in Turkey; other local CROs have limited services and outsourced work to us.” As he explains, “the Turkish clinical trial area has changed a lot since Omega CRO was founded; at the beginning we didn’t have a solid regulatory framework, then we had solid regulations but the timelines became too slow, and now we have optimal regulation with optimal timelines.” Regarding the current clinical trial environment, Özdemir admits Turkey is “still not very competitive, it is difficult for us to substantially increase the number of global trials we can attract... [However], there are some very good projects underway in line with the Vision 2023 goals, and the Ministry of Health recently hosted a workshop in Izmir on how to attract more clinical trials.”

Yet, one multinational has taken a strong interest in bringing high value R&D activities to Turkey, going beyond clinical trials and bringing basic drug research to Turkey. “AstraZeneca has signed a collaboration agreement with Koç University, that gave us responsibility for preclinical testing and research for a few candidate molecules, as well as access to their broader open innovation chemical library,” according to Burak Erman, head of the Drug Research Center at Koç University. AstraZeneca Turkey’s country president Pelin Erişiren Incesu explains that “some of the projects have progressed very well, and the Turkish scientists involved have travelled to AstraZeneca HQ in Cambridge to present their findings, and we remain confident that one or two of these projects will proceed to the clinical development phase, and maybe become the first drug of Turkish origin in the coming years.” AstraZeneca’s support of this project demonstrates that the company is “on the right track to building scientific leadership,” one of the three pillars of AstraZeneca’s current global strategy, according to Incesu.

**TURKISH INNOVATION**

Apart from R&D efforts in the field of biosimilars, several locals and multinationals are taking strong innovative steps. Mehmet Pisak, one of the former owners of Mustafa Nevzat, which was sold to Amgen in 2012, and now CEO of Imuneks Farma, contends “super-geneic product development makes a lot of sense for Turkish companies. Combination products are the starting point, which are very popular in Turkey right now, and we as Imuneks Farma have three of them with marketing...
authorization in Turkey. Further down the road, a few of the larger Turkish players might be able to develop a molecule from scratch.” Imuneks has four patents, two approved and two pending, for “a rare disease product... another is in ophthalmology, and two others are for antiviral products. The first two were just approved in the US and EU.” Pisak continues, “These are drug repositioning projects, where we took an existing molecule and targeted a new indication with a new formulation... We’re maybe three years away from bringing at least one of these products to market.”

Larger Turkish companies like Abdi Ibrahim and Nobel are also investing in innovation, with combination products being the best example of value added products that have reached the market; as Hasan Ulusoy, chairman of Nobel describes, “most R&D in Turkey is done in the context of generic development, while there is some product innovation in terms of combination products and improved formulations.” Abdi Ibrahim fits this description. CEO Süha Taşpolatoglu recounts that the company’s R&D unit has “developed several generic products which are the first generic versions of the molecule worldwide, and several of the products developed by our team are sold in Europe by our [multinational] partner companies,” and is beginning to make headway in “value-added product development, specifically in combination products; we have already launched our first [combination product] on the Turkish market and have others in development.”

Nobel is working to innovate on a higher level, as Ulusoy explains. “Nobel has started some elementary research for an original product, and in this respect I believe we are the only Turkish company to have invested so much in R&D. Currently this product is in a phase I clinical trial.”

According to CEO Ersin Erfa, Ceneturion is also working on “the development of a new orphan drug, a new molecule to treat pulmonary sarcoidosis... This new molecule is currently in phase III of clinical development, and we hope that it will become the first molecule to be developed by a Turkish company to reach the market, which should occur within the next two years.”

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**Biologics in the treatment of asthma**

Eosinophils are known to infiltrate the airways of some asthma patients and cause airway inflammation. AstraZeneca is developing a biologic that binds to the surface of eosinophils and recruits natural killer cells to remove them from circulation.
Strength From the Few
Rare disease supporters deliver inspiration and optimism—as well as promise of regulatory cooperation

Rare disease advocates seem to have something to say to the industry, “Our work is important and amazing. We have made great progress, but there is so much more to do!” This, or something catchier, could easily have been the slogan for this year’s summit held by the National Organization for Rare Disorders (NORD) in Arlington, Virginia, in October.

Amidst mounting industry rancor, a visit to the conference might be just what the doctor ordered for pharmaceutical executives who could use a reminder of the patient mission and how to achieve it through bold scientific research and cooperation. Given its inside the beltway locale, a day-trip for some politicians could also have been convenient and constructive.

Exceptional scientific breakthroughs are rife across the industry, including in many rare diseases, as this month’s pipeline report indicates. But there are four elements that were noticeably different at the NORD Summit, compared to many other pharma industry/medical conferences.

First, patient involvement is indispensable. It is clear that patient action, advocacy, and sacrifice is at the center of the success the industry has seen in rare diseases. Taking this as a cue, the conference organizers have plainly made patient participation fundamental. Their emotional and personal stories are one thing, but the real emphasis comes when the message resounds, that patients are essential for the entire drug development and treatment process. Success stems from years of sacrifice by patients and their supporters, who—though suffering through lifetimes of minimal relief—donated time, samples, genomes, etc., to build databases and natural histories. And don’t forget about those patients who suffered on placebo arms of trials.

Second, people dedicated to rare diseases exude optimism—this, in spite of their struggles and tragic accounts. There were numerous moments during the NORD event where it would have been difficult to find a dry eye in the audience. The overwhelming mentality is a sense of mission.

Third, regulators take a front and center seat in the rare disease dialogue. Surely, companies, regulators, and patients bump heads in the rare disease space, as in others. One needs to look no further than the always-contentious debate around early access and the political setting of “right to try.” The summit gives regulators a voice, and it’s clear that their participation is collaborative and constructive. The conference’s DC-adjacent venue and the presence of multiple representatives, many garbed in formal military uniforms, confer an air of civil discourse and service that is missed elsewhere. Though it should be noted, presentations by FDA officials, whose opinions are always their own and don’t represent the agency, have a way of sapping enjoyment from a room.

The optimism in rare diseases seems to spread to these regulators. With the political season heating up, the industry promises it will have a retort to those who seek to crush it on the profit motive and price gouging. Huge treatment prices in rare diseases are easy to point to. But maybe the industry can flip the rare disease example to its favor. It’s a complex issue, but one that NORD’s participants grasp. Hopefully, the rest of the industry is listening.©
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