Pharmaceutical Executive

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Pharmaceutical Executive

NOVEMBER 2014
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Pharma Science: It's Hard

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THERE IS GROWING OPTIMISM about the potential of medicines to manage—even cure—a growing number of once untreatable conditions. That's the simple takeaway from *Pharm Exec*'s annual review of what's coming up next from the industry's $60 billion pipeline of drugs in development. As contributing writer Josh Baxt notes in this month's cover feature, "immunotherapy is unlocking its promise as a safer way to fight cancer, we are seeing the first new treatments for heart failure since the 1980s, and gene therapy—the ultimate guarantor of personalized medicine—is finally approaching the clinic."

Yes, it's a good time to be a patient. The larger question is whether the times are as good for the industry that accounts disproportionately for the task of rendering basic science into therapeutically effective medicines, able to perform consistently across a target patient population. The truth is there are some real tears in the patchwork gauze that binds a new entry to the commercial market. Many of these fissures lie hidden from public view, characterized only in vague terms like long lead times to market and high "sunk" costs. Yet, combined, they amount to a smoldering challenge to the current approach to drug development, a silent reminder of the necessity to embrace a different, perhaps more frugal model.

Here are a few "grand challenges" that drug developers in this new world of science face in moving a compound forward, from bench to bedside:

While time-is-money problems continue to rise in late-stage development, initial work in de-risking an asset for human trials is also slowing progress. One major challenge is the failure of traditional animal models to keep pace with the proliferation of testable drug candidates in certifying whether such candidates are likely to work safely when transposed to humans. No compound can progress toward regulatory approval without this essential benchmark being met, yet the predictive capacity of the "oncomouse" and other genotyped rodent models—their ability to yield an objective clinical response—is still quite low. In key areas like cancer it is getting lower as researchers attempt to develop models that can accurately mimic the contours of ever more complex tumors. The result is lengthy delays in progressing assets to crucial Phase IIb work and beyond: scientists say it's one of the less recognized roadblocks in that race to de-risk.

Next, consider the mounting complexities in the conduct of clinical trials, as a new generation of biologic drugs demand significant investments in pinpointing and recruiting the right patient candidates; appropriate monitoring, across multiple sites; data retention and evaluation; and extraordinary levels of physician supervisory engagement. Trials centered on the "one drug/one condition" methodology are becoming irrelevant. To satisfy the exacting expectations of trial reviewers coping with compounds that embody new science and an unconventional therapeutic approach, drugmakers seek to cover many bases at once, leading to internal process irregularities, data silos, and mid-course protocol adjustment snags that the Tufts Center for the Study of Drug Development (TCSDD) estimates costs the industry $6 billion a year in unnecessary spending.

What happens after approval may be even more significant. A nod from the FDA is only the beginning of a mounting series of regulatory obligations designed to evaluate the safety, efficacy, and "medical need" for a medicine under real-world clinical conditions. These often involve the preparation of large-scale studies in multiple locations—or, alternatively, among highly selective small subpopulations—that can go on for years, exceeding even the length of the drug's patent and costing many millions of dollars.

Unfortunately, industry has failed to highlight what it is taking on to comply with these post-approval mandates. The long time frames for this work may also mean study conclusions are less relevant to the current state of therapy, which can lead to pressures for withdrawal of the product from the market. And how many promising drug development leads will be sidelined due to the priority all this post-approval work gives to the perspective of the regulator, whose role in many jurisdictions is morphing from simple registration approval to gatekeeper on pricing and reimbursement as well? What was once predictable is increasingly uncertain: the days when approval boundaries were fixed and finite, as exemplified by the slogan "We won, so we're done," are clearly over.

Finally, there are the usual competitive challenges, although this time the threat may be extramural, led more by countries than companies. China, with its huge market size and scale, is beginning to demonstrate the capacity to develop innovative drugs at lower cost than its Western equivalents. Science is not going to get any easier, so finding ways to economize through process innovations may end up being the stitch that saves the industry.

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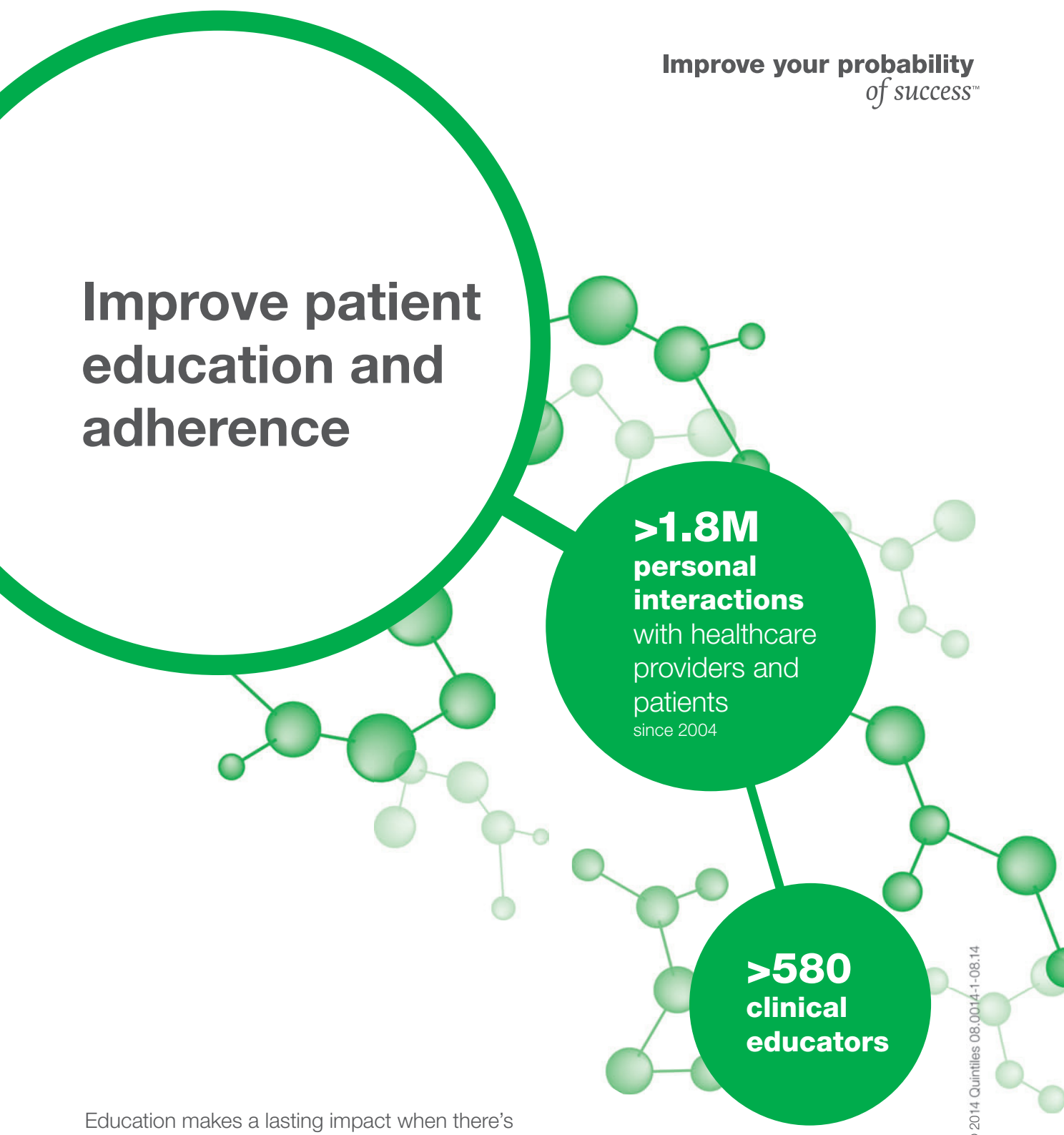

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On The Cover: Getty Images/pixelparticle

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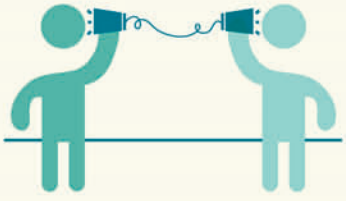

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2014 Emerging Pharma Leaders

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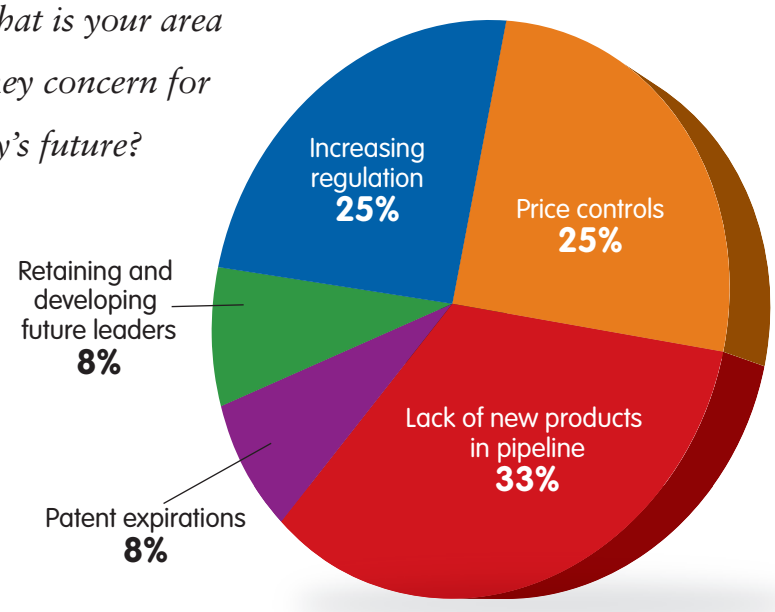
Most-read stories online: September 25 to October 24, 2014

Data Point

Poll data courtesy of online *Pharm Exec* readers between August 20 and August 30, 2014

Q: What is your area of key concern for the industry's future?



Readers Weigh In

Interesting statistics but incomplete. HIV drug consumption has increased, but what is that as a percentage of total drug benefit costs? Second, the average age of [Affordable Care Act] enrollee is 44 years, versus 37 years [for] private insurance, but what is the spread? Probably a lot of these people are above 50 years of age, typically when employers start to get rid of these "expensive" employees.

Sadiq A Khan, 10/23/14
"Pulling Back the Curtains on Obamacare Rx Usage"
bit.ly/1oQvOY7

The real problem that sales reps encounter is the inability to discuss off-label information, even if it is published in peer-reviewed journals, authored by acknowledged KOLs, and even may be accepted as a *de facto* standard of care. Reps are no longer seen as providers of new information about their drugs.

Tim Yu, 10/16/14
"Customer Engagement Isn't Just About Physicians: It's About Sales Reps Too?"
bit.ly/1D155un

The problem you exposed is educating the media and pharmaceutical companies to speak in this very same language of value.

Mike Pucci, 10/9/14
"The 'Value' of Rx's Under Obamacare"
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When The Greatest Risk Is Not Acting At All

Challenges, opportunities, strategies and regional insights from UPS's 7th Annual Pain in the (Supply) Chain survey

If there is a message in the 7th annual UPS Pain in The (Supply) Chain survey, it is that those companies sitting back adjusting familiar friction points need to act now and begin transforming their supply chains to meet the needs of a continually changing healthcare industry.

The next level of business growth will almost inevitably require implementing change. The goal is to create agile, efficient, and flexible supply chains to be a winner in today's global marketplace. To forgo acting may be the greatest risk of all.

The annual UPS Pain in the (Supply) Chain survey is a blind, in-depth phone survey conducted by TNS, on behalf of UPS. In 2014, between January and March, more than 530 healthcare executives in the U.S. and Canada, Western Europe, Asia and Latin America were queried. The respondents were senior-level decision makers, responsible for supply chain and logistics in the pharmaceutical, medical device and biotech industries. The surveys were conducted between January and March 2014.

The results identify untapped opportunities, top global markets targeted for expansion, and successful strategies to implement for growth.

The survey also outlines with surgical exactitude the challenges affecting healthcare delivery today. The top three being —regulatory compliance, managing supply chain costs, product security. This year, regulatory compliance surpasses last year's cost management (second place this year) with 66 percent of executives citing it as a top issue.

And how is the biopharmaceutical industry responding to these unique challenges? Logistics leaders who are already transforming their supply chain and executing their strategies by developing forward-looking initiatives, embracing risk and enabling growth in the new healthcare environment are taking steps to:

- form strategic partnerships to overcome challenges such as compliance, managing costs and accessing global markets;
- make significant investments in technology and/or investments in building in-house expertise to improve competitiveness and efficacy.

A planned technology investment enables better order flexibility and visibility as well as easier patient access through online ordering, and better protection for products moving through elongated supply chains.

TAKE ACTION: 4 STEPS TO SUCCESS

1. Assess the opportunities you haven't yet capitalized on, and set your goals
2. Consult experts to determine the supply chain you will need to achieve success (and plan for the unexpected, too).
3. Create a supply chain that is agile, efficient, and scalable.
4. Move quickly to capture opportunities in new markets—your competitors are likely doing the same.

Challenges at a critical juncture

The trends driving the changes in global healthcare are not going away. The population is growing, the median age is rising, and the demand for healthcare services around the world has never been greater.

Economic conditions still weigh on healthcare companies. This is particularly true in North America, which, to a degree, remains impacted by the recession and also in Latin America. This can result in tightened spending, other reductions and cutbacks.

Cost management, driven by regulatory reform, changing reimbursement models and profit pressures, still remains a top supply chain issue and yet, as shown by the drop in this and last year's ranking, the level of executive concern is declining continually.

Regulatory compliance stubbornly stays at the top of business and supply chain issues. A murky legislative outlook, varying and differing regulations, even in neighboring countries, make the issue more complex. The rules change, and keep changing.

Some healthcare executives report seeing success in addressing the challenges of regulatory requirements as well as cost management through partnerships that bring regulatory expertise.

Product protection, product integrity and product security is another area that is of crucial concern (46 percent of executives concurred). It has become more complicated as products become more complex and companies expand into emerging markets. This can mean an increasing number of hand-offs. Supply chain visibility is more acute. And temperature control becomes even more important. Among all supply chain executives, those in Asia-Pacific, 34 percent, expressed the most concern about product damage and spoilage.

Solutions for growth

Partnering and technology are effective antidotes to combating challenges in compliance, cost management and global market access. Planned technology investments can improve competitiveness and efficiency. And it is a top strategy to enable better product protection, visibility, and easier patient access through online ordering.

Leveraging both partnerships and technology can also aid in global growth and expansion, which often means a complicated regulatory environment and in emerging markets, an inadequate infrastructure.

New distribution opportunities

New distribution channels and strategies bring new opportunities—particularly with anticipated growth in home healthcare. Seeking ways to deliver better service at a lower cost, while also meeting the demands of the increasingly engaged and informed patients, the healthcare industry has created many decentralized care options, including home healthcare. According to executives surveyed worldwide, 30 percent of their products will support the home healthcare channel in the next seven to ten years.

For more information on the UPS Pain in the (Supply) Chain survey and to download a copy, visit www.ups.com/PITC.

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*Philipp Cremer, Martin Losch, and Ulf Schrader, "Driving a Transformation in Efficiency," Outpacing Change in Pharma Operations, McKinsey, 2010; Innovation and Continuous Improvement in Pharmaceutical Manufacturing, U.S. Food and Drug Administration, 2004.

Outrage Grows Over Drug Pricing

Insurers, physicians attack high-cost therapies in anticipation of specialty drug surge.

It may be time for pharmaceutical executives to devise a new rationale for drug pricing other than the need for high returns to support research and innovation. The important benefits of new cancer treatments and hepatitis cures diminish when physicians and patients find the medicines unaffordable, and Medicaid officials predict that soaring prescription drug outlays will undermine state education and safety net programs. Americans are angry that drugs cost less in Europe and object to funding biopharmaceutical development for the world. Last month's "60 Minutes" expose of soaring cancer drug prices was not a new story, but the discussion of "financial toxicity" for expensive oncology therapies clearly resonated with the public.

Public and private payers have been willing to pay high prices for certain new drugs and orphan therapies that offer important benefits for very sick and targeted patient populations. In an analysis in the October issue of *Health Affairs* on the value and cost of specialty drugs, James Chambers and colleagues at the Tufts' Center for Value and Risk in Health found that specialty drugs approved by FDA from 1999 to 2011 offered greater gains in quality-adjusted life-years (QALYs) compared to traditional medicines; although specialty drugs often cost more, they offer "reasonable value for money." Another article by researchers at Prime Therapeutics supported the use of specialty drug coupons to lower patient out-of-pocket costs and support adherence, even though that strategy discourages the use of cheaper drugs and ultimately boosts costs for insurers.

The important benefits of new cancer treatments and hepatitis cures diminish when physicians and patients find the medicines unaffordable.

Mounting opposition

But the specialty drug model was upended by approval of Gilead's Sovaldi, indicated to treat some 3 million Americans with hepatitis C virus (HCV) at $1,000 per dose. The heated debate over Gilead's pricing rationale has escalated since last month's approval of Harvoni, the company's new combination HCV pill that is even more expensive, although it could end up reducing total treatment costs. Insurers and payers see these new drugs as the tip of the iceberg for an anticipated surge in high-cost therapies for chronic conditions such as Alzheimer's and high cholesterol, which would stress health systems even more.

The attack on rising drug prices led by insurance companies has notable support from state Medicaid agencies, pharmacy benefit managers (PBMs), and consumer groups. At the annual fall Medicaid conference sponsored by America's Health Insurance Plans (AHIP), Sharon Levine of the Permanente Medical Group complained that costly specialty medicines will erode California's education system, and Michael Weinstein, president of the AIDS Healthcare Foundation, raised the specter of $10,000 pills: "If we don't draw the line somewhere," he warned, rising drug prices "will never end."

CVS Health chief medical officer Troyen Brennan noted at last month's *Health Affairs* briefing that pharmaceutical companies are "less than transparent" about pricing and development costs, and that Americans have a right to question whether industry's high revenues and profits reflect a reasonable rate of return.

Industry's response is continued emphasis on the value of life-saving therapies for individual patients, that prescription drugs account for a small portion of healthcare spending, and that further biomedical innovation is critical to improving health. Just after the "60 Minutes" broadcast, the Pharmaceutical Re-

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search and Manufacturers of America (PhRMA) released a report on nearly 800 cancer medicines and vaccines in development, along with an analysis of failed cancer drugs over the last 15 years to illustrate the many costly setbacks involved in discovering new treatments. And a new study from the Partnership to Improve Patient Care warns that alternative payment models, such as bundled payments, medical homes, and accountable care organizations, could diminish patient choice and impose "one-size-fits-all" cost containment tools.

Seeking new strategies

Many experts thus are looking for new ways to address these issues. Mark McClellan of the Brookings Institution proposed at the AHIP conference that "better evidence" on which drugs are more effective could support higher prices and lead to new pricing models for personalized medicines. At the *Health Affairs* briefing, Peter Bach of Memorial Sloan Kettering, who was featured in the "60 Minutes" report, urged a serious rethinking of coinsurance strategies and an end to Medicare Part B drug distribution, which tends to encourage physicians to administer high-cost therapies.

There's much discussion about altering how Medicare pays for drugs covered by Part D. And the Medicare Payment Advisory Commission (MedPAC) has been assessing the viability of a "least costly alternative" (LCA) approach that would align payments for certain Medicare Part B drugs administered in doctors' offices to the least expensive medicine in a class, an admittedly tricky approach, which was applied to a handful of Part B drugs between 1995 and 2010, but halted by legal action.

A recent conference on ways to "Turn the Tide Against Cancer" sponsored by the Personalized Medicine Coalition ended with a frank discussion of cost containment pressures. Stephen Eck, vice president of Astellas Pharma Global Development, described the complexities of drug pricing: that R&D costs are incurred long before a drug comes to market when it's hard to know it's full effect and value, and that current prices actually pay for the next drug development program—not the last one.

Richard Schilsky, chief medical office of the American Society of Clinical Oncology (ASCO), urged an end to all the finger-pointing between pharma and insurance companies over high co-pays and high prices. He suggested a "value pricing" approach that allows different prices for different uses of the same drug, depending on documented effectiveness for each indication. Aetna medical officer Michael Kolodziej agreed that it's probably better to examine the "global cost of care" than the "sticker price" of drugs. And CancerCare CEO Patricia Goldsmith complained that the high cost of drugs and biologics should not be the "lightening rod" in all discussions about the high cost of care.

Pharmaceutical executives might agree, but more transparency on pricing methods and unbiased assessment of the varying value of drugs is key to gaining public understanding of this complex market. PE

Generics lose low-cost luster

Inexpensive generic drugs are the good guys in the drug-pricing world, long applauded for facilitating patient access to new treatments and for helping to moderate U.S. spending on drugs and healthcare. Now payers are complaining that some widely used generics are posting thousand-fold price hikes, many related to shortages in active ingredients and manufacturing problems that reduce the number of suppliers.

The resulting sticker shock for consumers and profit squeeze on pharmacists has instigated a backlash and a Congressional investigation into "staggering price increases" for ten leading generics such as albuterol, tetracycline, doxycycline, and pravastatin. Reps. Bernie Saunders (I-Vt.) and Elijah Cummings (D-Md.) have sent letters to 14 firms, including Actavis, Dr. Reddy's, Endo, Mylan, Sun, and Teva, requesting information on gross revenues, manufacturing and ingredient costs, sales and profits, reasons for price increases, and comparable prices in foreign countries. The Generic Pharmaceutical Association (GPhA) objected that overall generic drug prices have fallen, and that the ten drugs boosting prices are just a few isolated cases in the vast generics market. But insurers are looking at higher co-pays and formulary tiers to manage spending on generics, just as they do for brands.

EMA—a Pioneer Permanently At Bay

Agency's plan for reporting clinical trial data has sparked strong reactions from health campaigners, industry, and patients.

The European Medicines Agency (EMA) really is between a rock and a hard place. Its earnest efforts to satisfy the critics who accuse it of obsessive secrecy seem to do little more than open it up to further criticism for not having done enough. And at the same time, drug firms—and many patient groups—become increasingly wary of the implications of the agency's direction of travel.

The agency might have expected that the latest stage in this continuing saga—the publication in October of its plan for proactive release of clinical reports—would receive a warm welcome. The agency aimed to assuage the appetites for data disclosure, and also to mollify the patients and drug producers who are anxious, each for their own reasons, to maintain a minimum degree of privacy. The plan is, after all, a judicious blend of ambition and caution. It goes further—the agency claims—than any other drug regulatory authority in providing access to the information on which marketing authorization decisions are based. Yet it simultaneously offers some safeguards for industry and some discretion for trial subjects.

'Conspiring with industry'

But the outcome is far from a roaring success. The critics continue to allege that the agency is conspiring with industry to conceal the important data. Industry says it needs to see how the plan works. And patients want guarantees of protection of their data, and more of a say in its functioning.

The most strident reaction has come from health campaigners, who have pointed to what they see as crippling deficiencies—a long list of historic failings that have now been consolidated by the EMA's new policy, so that they will stretch into the future too. A coalition of health campaigners, health insurance agencies, doctors and academics says that "for more than a decade, the EMA has failed to comply with EU rules on freedom of information," by neglecting to set up a register of documents that it holds—making it difficult for citizens to determine which document to request. The result, they say, has been endless exchanges with the EMA before documentation is provided.

The critics continue to allege that the agency is conspiring with industry to conceal the important data.

The coalition consists of well-respected and well-informed organizations—although all with a strong declared interest in protecting the patient, the citizen, and independent research: Association Internationale de la Mutualité, the Medicines in Europe Forum, Health Action International-Europe, the International Society of Drug Bulletins, and the Nordic Cochrane Center. They say the new policy will not provide adequate transparency. The criticisms center on the scope of the EMA plan: it will cover the reports only of trials submitted in support of centralized marketing authorization procedure, and it offers no proactive access to clinical reports for medicines already on the market. In addition, the redaction it provides for "can hinder the interpretation of data (e.g., in the interpretation of a serious harm narrative) or delay access to information of public interest (e.g., redaction of results on exploratory endpoints)," they argue. Allowing redaction is a licence for "censorship by pharmaceutical companies under the guise of protecting commercial confidentiality," they say: "The policy gives pharmaceutical companies the upper hand in deciding the contents of the clinical reports by allowing them to redact data." And they fear that companies will adjust the content of their clinical study reports to conceal as much as possible: "They will be written and structured in such a way as to withhold vital details of a pharmaceutical drug's effects or present them in the best possible light."

Compounding a felony

To compound the alleged felony, the EMA has abandoned other plans, announced in November

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

2012, to routinely require pharmaceutical companies to submit all original clinical trial data in a format that would allow the EMA to re-analyze the data, complain the critics. This means that a medicine can still be approved by the EMA on the basis of incomplete evidence, say the campaigners. Pierre Chirac, coordinator of the Medicines in Europe Forum, comments: "It seems that the EMA has found an easy solution to avoid having to release much clinical data: by just not requiring it from pharmaceutical companies in the first place…" At the very least, as some small compensation, the EMA should now proactively provide a numbered, standardized table of contents for clinical study reports (including a list of appendices and attachments containing information on study design, conduct or results), so that researchers can identify relevant additional information that they might wish to request under freedom of information rules, says the coalition.

The critics have the wind in their sails. The EU Ombudsman, Emily O'Reilly, now on the brink of a further term of office and acclaimed for her energy, has already announced her engagement. She says she will monitor how the EMA deals with access to documents requests, and will verify the justification for the redaction of information and the conditions attached to gaining access to documents. The Ombudsman's office has had the EMA in its sights for a long time. "Transparency is a vital means by which EMA can ensure the accuracy of its decisions," it said earlier this year, and transparency "serves to foster scientific discussion and progress, by enabling independent scientists to scrutinize the conclusions of EMA, and the data and arguments taken into consideration by EMA when reaching those conclusions."

Support for disclosure

Further support for the pro-transparency camp is sure to come from the left wing of the European Parliament, now jubilant at its successes in resisting the shift of pharmaceutical policy (and control of the EMA) from the health portfolio to the industry portfolio in the new European Commission. And the new health commissioner, Vytenas Andriukaitis, is likely to be respectful of the views of the strident MEPs who have led that campaign, and accordingly vigilant in defending the information rights of the public and independent researchers.

On top of that, the World Health Organization (WHO) has just issued a statement supporting the disclosure of clinical trial results, to enhance transparency for the public. It has launched a public consultation on its official position—which has already been welcomed by the UK's prestigious Health Research Authority (HRA). Tom Smith, HRA's director of quality standards and information, has greeted the WHO initiative as "a key step" along the road to seeing "all clinical trials results made available globally with parity in timescales." This, he added, would boost public confidence and reduce waste in research.

WHO's statement is a follow-up to the International Clinical Trials Registry Platform that it established to improve research transparency nearly a decade ago, based on its conviction that "the registration of all interventional trials is a scientific, ethical, and moral responsibility." This scheme has, however, proved insufficient, and WHO is now beefing up its approach. "Concerns have been raised that there may be selective publication of trials dependent on their results, with particular concern that trial results which may be viewed as 'negative' are less likely to be submitted, or accepted, for publication in the scientific literature or made public in other ways," it says.

"Multiple analyses have confirmed that a substantial number of clinical trials remain unreported several years after study completion, even in the case of large randomized clinical trials," states WHO. So it is now insisting that "all clinical trial registry sites are to be updated as necessary to include final enrollment numbers achieved, and the date of actual study completion." Trial results are to be reported within 30 months of the study completion date, both through submission for publication in a peer reviewed journal and through an open access mechanism. Key outcomes are also to be made publicly available by posting on the primary clinical trial registry. And it's not over yet. WHO also says it is "actively engaged with multiple initiatives related to data sharing, and supports sharing of health research datasets whenever appropriate."

Battling the noise

On every front, the EMA risks looking as if it is dragging its feet rather than leading the pack in the search for appropriate transparency. At a recent hearing on clinical trials data disclosure in the European Parliament, the EMA executive director, Guido Rasi, was quietly composed and confident in setting out the complex pressures and duties that EMA has to balance as it moves into a new era of access. But in a sound bite-dominated world, where it is often easier to transmit radical positions than calibrated compromises, even the equable Rasi was less compelling to most of the audience than the critics of the EMA approach. PE

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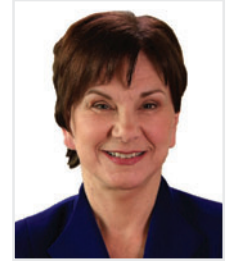

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2015 PIPELINE REPORT: Burning Bright

The science of drug discovery is back on script—and the stars are cued up for a new generation of breakthrough therapies. Patients are poised to benefit, but is pharma ready to raise its game and cut a deal with all those "prove it to me" payers?

By Josh Baxt

Tracking new therapies as they wind their way through development, regulatory approval, and payer acceptance can be like waiting for paint to dry and then repainting in a different color. It's a slow process and far from linear.

This is especially true for potentially groundbreaking drugs, disruptive technologies that completely upend markets and patient care. The lag time between that first flickering glimmer of hope and an accepted therapy can be measured in decades. And, all too often, agents that seem hopeful in the lab and early clinical trials fizzle on further investigation.

But then there are those rare moments when the stars align and truly astounding therapies make their way into the world, providing improved care and big returns. In the next few years, cancer immunotherapies seem likely to enter the pantheon of big winners. And they may not be alone. Besides the buzz around a cure for hepatitis C virus, there are exciting drugs for heart failure and cholesterolemia coming into play. On a smaller scale, companies are embracing new therapies for rare diseases. Stem cells are making real forays into late-stage trials.

This year's pipeline report will check in on these emerging technologies, as well as potential therapies to address metabolic and neurodegenerative diseases. There's a lot to like in the pipeline and more than a little competitive drama to make it really interesting.

Immuno-oncology: The elegant solution

For Trekkers, there's nothing better than watching a Klingon or Romulan ship lose its invisibility cloak and get blasted out of space. On the cellular level, similar action is driving the excitement around programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) checkpoint inhibitors: the opportunity to reveal cancer and unleash the immune system against it.

"There's genuine enthusiasm among oncology experts," says Seamus Fernandez, managing director of Major and Specialty Pharmaceuticals at Leerink Partners. "There's evidence of activity in more than five different tumors and signals of activity in as many as 14. We forecast a $36 billion immuno-oncology market by 2025."

That's a large pie and there's been a lot of jostling to get the biggest piece. Bristol-Myers Squibb's cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor *Yervoy* (ipilimumab) was first out of the gate, but there are several other agents poised to hit the market.

In September, Merck's PD-1 blocker *Keytruda* (pembrolizumab) received accelerated approval from the FDA to treat melanoma and the company is researching the drug against non-small cell lung cancer (NSCLC) and other indications.

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In its World Preview 2014 Outlook report, EvaluatePharma forecasts *Keytruda* sales of $4.06 billion by 2020.

That's a great start, but it's unclear whether Merck's advantage will hold out over the long haul. The competition will be fierce in the PD-1/PD-L1 space. With the huge potential market, this could be the equivalent of the Oklahoma land rush for the usual pharma titans. However, Stephanie Hawthorne, senior director at Kantar Health, notes that, for now in melanoma, Merck is in the driver's seat compared to BMS's PD-1 inhibitor *Opdivo* (nivolumab), which is a few months (or possibly longer) behind *Keytruda* in the US.

"It's a big advantage for Merck being first-to-market," says Hawthorne. "Based on the available data, they both look really efficacious, and they're fairly well tolerated compared to *Yervoy*. BMS's saving grace might be the combination of *Opdivo* and *Yervoy* they are studying. The survival data we've seen for it so far is really impressive, and that could trump Merck's lead."

Hawthorne's point was underscored in late September when BMS released data at the European Society for Medical Oncology (ESMO) showing that *Opdivo* achieved a 32% response rate against advanced melanoma in patients who had previously been treated with *Yervoy*. The control group, which received traditional chemo, had an 11 % response.

While *Keytruda* was first in the US, *Opdivo* was approved for melanoma in Japan in July, under a deal with BMS partner Ono Pharmaceuticals. The ESMO data will only support BMS's showing in the US. The FDA has given *Opdivo* fast track designation in NSCLC, melanoma, and renal cell carcinoma (RCC) and breakthrough therapy designation for Hodgkin's lymphoma. In September, BMS announced that both the FDA and European Medicines Agency (EMA) have accepted *Opdivo* for accelerated review for melanoma. The FDA PDUFA date is March 30, 2015.

"*Opdivo* is the most valuable pipeline drug in development at the moment," says Lisa Urquhart, editor of Evaluate's editorial team, EP Vantage. "The data from studies is showing some impressive advances in both overall survival and disease progression."

EvaluatePharma pegs *Opdivo*'s potential sales at $6 billion by 2020. The company believes *Opdivo* could be approved for melanoma in the US next year, but Hawthorne has set her own expectations at early 2016.

That's in melanoma. *Opdivo* may even have a more clear-cut advantage in being first-to-market for NSCLC, where BMS has already submitted its drug for approval while Merck is still completing Phase III trials.

A crowded field

The PD-1/PD-L1 approach is generating a lot of enthusiasm for good reason. Early results have shown great efficacy in many indications, including underserved areas, such as bladder and head and neck cancers. The possibility of producing an agent that can target multiple cancers is raising heart rates throughout the pharma industry.

"These drugs are all across the board," says Hawthorne. "I'm not sure there's a tumor type that's not being touched: renal cell cancer, head and neck, bladder, and Hodgkin's lymphoma. It's just an indication of how huge and impactful these could be for patients."

Again, this is underscored by Merck results, also released at ESMO, which showed a 24% response rate for *Keytruda* against bladder cancer.

Genentech/Roche's PD-L1 offering, MPDL3280A (RG-7446), is in trials for NSCLC, melanoma, RCC, and bladder cancer. The company received breakthrough designation for this last indication. EvaluatePharma puts sales at $2.93 billion by 2020, while the Thomson Reuters Cortellis database puts them at $1.2 billion by 2019.

MedImmune/AstraZeneca is also in the race with PD-L1 drug MEDI-4736, primarily targeting NSCLC. Also shared at ESMO, a small 18-person study showed a 28% response to MEDI-4736 combined with the CTLA-4-directed antibody tremelimumab. Cortellis projects MEDI-4736 sales at close to $1.1 billion by 2019.

"We're just at the tip of the iceberg for immuno-oncology, but the enthusiasm is certainly warranted because of the kinds of responses and the tumors being opened up," says Fernandez. "The field is about as exciting and confusing as you could possibly imagine."

DRUG NAME:	Keytruda
COMPANY:	Merck
PHASE:	Launched for melanoma
LAUNCH WINDOW:	September 2014
ESTIMATED SALES:	Blockbuster

DRUG NAME:	Opdivo
COMPANY:	Bristol-Myers Squibb
PHASE:	III
LAUNCH WINDOW:	2015
ESTIMATED SALES:	Blockbuster

DRUG NAME:	MPDL3280A
COMPANY:	Genentech/ Roche
PHASE:	III
LAUNCH WINDOW:	2017
ESTIMATED SALES:	Blockbuster

DRUG NAME:	MEDI-4736
COMPANY:	MedImmune/ AstraZeneca
PHASE:	III
LAUNCH WINDOW:	2017
ESTIMATED SALES:	Blockbuster

In the next few years, cancer immunotherapies seem likely to enter the pantheon of big winners.

DRUG NAME:	blinatumomab
COMPANY:	Amgen
PHASE:	III
ESTIMATED SALES:	$325 million

DRUG NAME:	veliparib
COMPANY:	AbbVie
PHASE:	III
ESTIMATED SALES:	$350 million

DRUG NAME:	rucaparib
COMPANY:	Clovis/Pfizer
PHASE:	II
ESTIMATED SALES:	$414 million

The combo conundrum

With these fantastic response rates in aggressive cancers, how will PD-1/PD-L1 inhibitors redefine patient care? As monotherapies? In combination with other types of immuno-oncology drugs? Or will they be combined with the new generation of targeted chemotherapies?

"The best-case scenario, these agents are working in 35 to 50% of melanoma patients as single agents," says Fernandez. "Worst-case scenario, maybe they're working in 15 or 20%. There's a strong conviction that multiple mechanisms are going to be relevant in various different tumors."

How this will play out is subject to much debate. If Fernandez's more optimistic scenario proves accurate, these checkpoint agents could be extremely successful monotherapies, which could have a profound impact on standards of care.

"This could be very disruptive," says Hawthorne. "Whereas you're used to treating lung cancer with cisplatin or carbo-taxol first line, you might get *Opdivo* and that could push those drugs out."

Hawthorne anticipates that both clinical and commercial factors will drive companies to test their more traditional therapies in combination with the emerging checkpoint inhibitors.

"If the drug has the potential to displace you, then it makes sense to go in combination with it," says Hawthorne.

In addition, there's the long-term possibility of pairing a PD-1/PD-L1 with emerging immunotherapies that target different mechanisms. Just over the horizon, chimeric antigen receptor (CAR-T) therapies could make a big impact. Unlike PD-1/PD-L1 inhibitors, which unchain immunity, CAR-Ts activate the immune system, which offers intriguing possibilities, as well as possible dangers.

"My wariness would be around the potential side effects," says Hawthorne. "If you're simultaneously upregulating the immune system and taking the brakes off, that could go kind of crazy."

At this point, Novartis is first in the CAR-T line with CTL019, which received breakthrough designation from the FDA in July for acute lymphoblastic leukemia (ALL). The drug is currently in Phase II trials.

However, CAR-T therapy may not have an easy path. A Juno Therapeutics/Memorial Sloan-Kettering study for aggressive non-Hodgkin's lymphoma (NHL) was halted recently after two patients died from cytokine release syndrome, one of the apparent risks of taking the brakes off the immune system. While the study was only delayed, this event underscores potential concerns about CAR-T therapies.

Another interesting immuno-oncology therapy is Amgen's blinatumomab, a bi-specific T-cell engager (BiTE). Blinatumomab received breakthrough therapy designation for ALL in July, and Amgen has filed for early approval. At Leerink Partners' Healthcare Insights Conference in July, a number of experts expressed their belief that this drug is an interesting proof-of-concept; however, they were also concerned about neurotoxicity. Thomson Reuters puts potential sales at $325 million by 2019.

There are too many immunotherapies to list here, which is great news for cancer patients. Ultimately, PD-1/PD-L1 may form the backbone for a variety of combinations. This is based on efficacy, as well as a complementary mechanism of action, but there's also a practical measure. With so many different combinations, it would be virtually impossible to test them all.

"The stakes get a lot more interesting and a lot more confusing," says Fernandez. "We are going to see a significant number of mixed successes and disappointments as we move forward with these different combinations."

Targeted oncology agents

While immunotherapies may hold the greatest upside, there are still a variety of more traditional treatments in the oncology pipeline.

First on the list are the poly ADP ribose polymerase (PARP) inhibitors, which encourage cancer cell death by limiting this DNA-repair enzyme. They include veliparib from AbbVie; rucaparib from Clovis Oncology/Pfizer; *Lynparza* (olaparib) from AstraZeneca; and BMN-673 from BioMarin. Their oral administration makes them particularly exciting.

Veliparib is being developed for triple-negative breast cancer and NSCLC. The drug showed a 52% response rate against breast cancer in a study that combined it with car-

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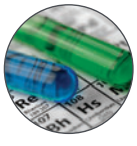

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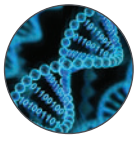

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DRUG NAME:	palbociclib
COMPANY:	Onyx/Pfizer
PHASE:	Filed
ESTIMATED SALES:	Blockbuster

DRUG NAME:	LCZ696
COMPANY:	Novartis
PHASE:	III
LAUNCH WINDOW:	2016
ESTIMATED SALES:	Blockbuster

DRUG NAME:	Serelaxin
COMPANY:	Novartis
PHASE:	Filed
ESTIMATED SALES:	$484 million

boplatin and paclitaxel. AbbVie recently announced a pivotal Phase III study for patients with advanced breast cancer. The company is also conducting a Phase II trial for NSCLC. Thomson Reuters projects sales at $350 million by 2019.

Meanwhile, in a Phase II study, rucaparib showed a 93% disease control rate in BRCA-positive ovarian cancer. Thomson has rucaparib at $414 million by 2019.

Clovis has also earned breakthrough designation for its epidermal growth factor receptor (EGFR) blocker CO-1686 for lung cancer. At the 2014 ASCO Annual Meeting, Clovis unveiled excellent progression-free survival in a combo Phase I/II study.

The company will have major competition from AstraZeneca's AZD9291, which targets both EGFR and the resistance mutation T790. AstraZeneca is partnering with Roche, and the drug is currently in pivotal trials. They plan to file with regulators in the latter part of 2015, which seems like a long way off. Thomson Reuters estimates $761 million in sales in 2019.

Then there are the cell cycle regulating cyclin-dependent kinase 4 (CDK4) and CDK6 inhibitors, which show great potential for adjuvant treatment. At the front of the pack is Onyx/Pfizer's palbociclib. Pfizer has recently submitted a new drug application (NDA), in combination with letrozole, to treat advanced ER-positive, HER2-negative breast cancer. Data submitted at the AACR Annual Meeting showed a progression-free survival of 20.2 months. EvaluatePharma predicts palbociclib will have worldwide sales in the $2.95 billion range by 2020. Thomson Reuters Cortellis puts sales at $2.02 billion in 2019.

Another CDK4/CDK6 candidate is Eli Lilly's abemaciclib for metastatic breast cancer and NSCLC. Cortellis forecasts $306.2 million for that drug.

A revolution in heart failure

Heart failure is an underserved health area that is continuing to grow. Decision Resources Group recently estimated it will expand from $2.9 billion in 2013 to $8.9 billion in 2023. Breakthroughs have been limited for some years, so the field is wide open for promising therapeutics.

"Heart failure is very common and getting more common, very expensive in terms of comorbidities and really underserved," says Les Funtleyder, a healthcare portfolio manager at E Squared Asset Management and member of *Pharm Exec*'s Editorial Advisory Board.

Few drugs are generating more enthusiasm than Novartis' heart failure and hypertension treatment LCZ696. The drug has novel mechanisms, combining sacubitril to preserve peptides that lower blood pressure and valsartan to improve vasodilation. There haven't been any major improvements in heart failure therapies in decades. EvaluatePharma puts sales at $1.3 billion by 2020, while Thomson Reuters has them at $1.8 billion in 2019. Both estimates may be conservative.

Data from a pivotal Phase III trial showed the drug reduced the risk of death by 20%, compared to an angiotensin-converting-enzyme (ACE) inhibitor, as well as dramatically reducing the risk of hospitalization. There's a lot of excitement that this new drug could supplant ACE inhibitors and ARBs.

"We're forecasting $6 billion of peak sales, but that number could be low by a factor of 50% or even a 100%," says Seamus Fernandez. "LCZ696 could be a *Plavix*-like product."

This enthusiasm appears to be widespread.

"LCZ696 has been described as a game changer and there are some that believe that because of its mortality benefit it should become the standard of care replacing ACE inhibitors and ARBs, especially given its very clean safety profile," says Urquhart. "The market was also quick to wake up to its potential and after the Paradigm-HF trial was stopped early in March because of its conclusive benefits."

By contrast, Novartis' other heart failure drug has hit hard times. In May this year, the FDA rejected Novartis' biologics license application (BLA) for *Serelaxin*. A synthetic human relaxin 2 hormone, *Serelaxin* has breakthrough designation but the FDA needed more efficacy data for approval and had issues with the trial design. Novartis has been conducting a large Phase III trial and hopes the results, expected in 2016, will sway the FDA.

Serelaxin is a tantalizing prospect for both Novartis and analysts. In addition to the potential one-two punch with LCZ696, acute

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COMPANY:	Sanofi/Regeneron
PHASE:	III
ESTIMATED SALES:	Blockbuster

DRUG NAME:	evolocumab
COMPANY:	Amgen
PHASE:	III
LAUNCH WINDOW:	2016
ESTIMATED SALES:	$777 million

DRUG NAME:	bococizumab
COMPANY:	Pfizer
PHASE:	III
LAUNCH WINDOW:	2018
ESTIMATED SALES:	$231 million

DRUG NAME:	anacetrapib
COMPANY:	Merck
PHASE:	III
LAUNCH WINDOW:	2017
ESTIMATED SALES:	$759 million

DRUG NAME:	evacetrapib
COMPANY:	Lilly
PHASE:	III
ESTIMATED SALES:	$373 million

DRUG NAME:	Toujeo
COMPANY:	Sanofi
PHASE:	Filed
LAUNCH WINDOW:	2015
ESTIMATED SALES:	Blockbuster

DRUG NAME:	Basaglar
COMPANY:	Lilly/Boehringer
PHASE:	Tentative approval
LAUNCH WINDOW:	Unknown
ESTIMATED SALES:	$401 million

heart failure is a serious unmet need, with clinicians looking for successors to beta blockers, developed in the 1960s, and ACE inhibitors, developed in the '80s.

"There hasn't been a product to advance the in-hospital treatment for heart failure in somewhere between 30 and 50 years," notes Fernandez.

Fernandez styles *Serelaxin* a dark horse. However, if Novartis can get past the regulatory hurdles, Leerink Partners projects *Serelaxin* could be worth two to three billion dollars. By contrast, EvaluatePharma puts its sales at $484 million by 2018.

Raising HDL, Lowering LDL

There's a lot of work being done on LDL cholesterol, and a lot of skepticism to match. There could be an upcoming battle between proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors and cholesterylester transfer protein (CETP) inhibitors, or not. Both approaches have great potential and flaws. The PCSK9 inhibitors seem to have a cleaner path towards approval. However, administration and compliance could be an issue.

"You're introducing an injectable and an antibody to treat an asymptomatic condition," says Fernandez. "People tend to be less compliant."

Leerink Partners believes there's a potential $10 billion worldwide market by 2030 for the four leading PCSK9 inhibitors from Amgen and Sanofi/Regeneron—the obvious leaders—followed by Pfizer and Lilly. The investment bank projects $4 billion by 2020.

Sanofi/Regeneron's alirocumab and Amgen's evolocumab seem pretty evenly matched, and the market may respond in kind. EvaluatePharma puts sales by 2018 at around $1 billion and $777 million, respectively.

Pfizer's bococizumab showed great results in a Phase IIb trial, significantly reducing LDL in patients also treated with statins. EvaluatePharma puts their sales at $231 million by 2018.

CETP inhibitors are administered orally but must contend with the long shadows of Pfizer's torcetrapin, which, unfortunately, had deadly side effects, and Roche's dalcetrapib, which simply wasn't effective. However, Merck's anacetrapib and Lilly's evacetrapib seem to be better at raising HDL and lowering LDL and are worth watching. Thomson Reuters has anacetrapib sales at $759 million by 2019 and evacetrapib at $373 million in the same time period.

"There's more consistency on the PCSK9 side," says Fernandez. "We don't have the same evidence with CETP inhibitors. However, if they work, and they may simply work by lowering LDL, they are oral products and might be the larger class."

Diabetes and obesity

In the immediate future, it seems like the diabetes market will be more evolutionary than revolutionary, governed by refinements in insulin delivery rather than major breakthroughs. Still, there are improvements to be made and healthy profits on top of that.

Case in point, Sanofi's *Toujeo* (insulin glargine), a reformulated long-lasting insulin, could preserve the company's income stream as *Lantus* loses patent protection. The FDA accepted *Toujeo*'s NDA in July, and approval is expected in the first half of 2015. EvaluatePharma's projection comes in at $1.4 billion in sales by 2018. Thomson Reuters forecasts $1.6 billion by 2019.

Lilly/Boehringer's insulin glargine, *Basaglar*, was given tentative approval by the FDA in August, but Sanofi is claiming patent infringement. As a result, approval has been delayed for up to 30 months while the case makes its way through the courts. EvaluatePharma projects $401 million in sales by 2018.

Lilly/Boehringer are also working on insulin peglispro, an insulin analog for type 1 and type 2 diabetes. A recently concluded trial showed daily treatment compared favorably to insulin glargine. Lilly plans to submit insulin peglispro in early 2015. EvaluatePharma estimates sales of $406 million by 2018.

Focusing on type 2 diabetes, Lilly's long-acting glucagon-like peptide-1 (GLP-1) agonist *Trulicity* (dulaglutide) received FDA approval in September. GLP-1 is a hormone that balances blood sugar, making it a particularly tempting target for type 2 diabetes treatments. With EvaluatePharma projecting sales of $912 million by 2018, *Trulicity* could be bad news for Novo Nordisk and AstraZeneca.

"We think *Trulicity* could be a $1.5 billion drug and a meaningful competitor to Novo's *Victroza*," notes Fernandez. "I think it's going to do a lot of damage to AstraZeneca's *Bydureon*."

However, Novo has big plans for *Victoza* (liraglutide), which has recently been found safe and effective against obesity. In September, an FDA panel voted to recommend the drug for approval for that indication.

Perhaps more interesting, Novo has combined liraglutide with long-lasting insulin degludec (*Tresiba*) to create *IDegLira* for type 2 diabetes. Recent data have shown the drug works better than liraglutide and insulin degludec alone. Thomson Reuters puts *IDegLira* at $815 million by 2019. EvaluatePharma estimates $517 million by 2018.

Merck's omarigliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor to treat type 2 diabetes, is continuing through fairly massive Phase III trials. Taken weekly, the drug may reduce glucose as well as daily treatments. EvaluatePharma pegs sales at $412 million by 2018.

Zafgen's obesity drug *Beloranib*, which modulates fatty acid metabolism, is turning heads. A Phase II trial in 2013 produced rapid weight loss in severely obese patients and was well-tolerated. An effective weight loss drug with few side effects could have tremendous potential. This is definitely one to watch.

Neurodegenerative diseases

It would be wonderful to highlight a number of promising agents that could improve cognitive function in Alzheimer's disease patients. Billions have been spent on such treatments, most of them targeting amyloid plaque, and none of them have come through.

"There are so many bodies on the side of the road, it's almost as if the safe thing is to bet against any drug trying to affect cognitive function in Alzheimer's disease," says Ritu Baral, senior analyst, Biotechnology Equity Research managing director at Cowen and Co.

While there's no joy on the disease-modifying side, there are other efforts to mitigate some of the symptoms associated with Alzheimer's and other neurodegenerative conditions. Avanir's AVP-923, which combines ordinary dextromethorphan with the heart rhythm treatment quinidine, may have promise to treat the agitation associated with Alzheimer's. Avanir released positive Phase II results in September and is meeting with the FDA and EMA to discuss next steps.

"Agitation is the No. 1 driver behind hospitalization and institutionalization for Alzheimer's disease," notes Baral. "Agitation and aggression make it impossible to care for patients in the home setting."

Otsuka and Lundbeck are working on brexpiprazole for schizophrenia and major depressive disorder (MDD), as well as Alzheimer's-related agitation. The FDA has accepted the NDA for schizophrenia and as an adjunct treatment for MDD; the PDUFA date is set for July 2015. Thomson Reuters predicts potential sales of $1.43 billion by 2019. EvaluatePharma pegs sales at $763 million by 2018.

The pipeline is more promising in multiple sclerosis, as these drugs can target the underlying immune response. For example, Genentech/Roche's CD20 inhibitor ocrelizumab for relapsing-remitting MS is currently in Phase III trials and has been shown to reduce inflammatory brain lesions. Ocrelizumab is projected by EvaluatePharma to sell around $355 million by 2018. Thomson Reuters is a bit more bullish at $578 million by 2019.

Meanwhile AbbVie and Biogen Idec are working on the IL-2 receptor inhibitor *Zinbryta* (daclizumab), which treats relapsing-remitting MS. Recent data showed patients on the drug experienced a significant reduction in relapse when compared to *Avonex*, which had $3 billion in sales in 2013. EvaluatePharma projects $320 million by 2018 for *Zinbryta*, while Thomson Reuters goes higher at $829 million by 2019.

Bioden Idec's *Plegridy* was recently approved in the US as a weekly replacement for the daily Avonex. However, analysts are not universally enthusiastic about its prospects.

"The drug is approved in Europe and was supposed to be the natural, longer-acting successor to *Avonex*, which came off patent last year," says Lisa Urquhart at EvaluatePharma. "However, the lure of fortnightly dosing over weekly Avonex does not appear to be floating too many boats, and consensus sales forecasts for the drug have fallen significantly recently. At the moment, they are $537 million in 2018, nowhere near the $3 billion *Avonex* pulled in last year."

DRUG NAME:	insulin peglispro
COMPANY:	Lilly/Boehringer
PHASE:	III
LAUNCH WINDOW:	2016
ESTIMATED SALES:	$406 million

DRUG NAME:	Trulicity
COMPANY:	Lilly
PHASE:	Approved
LAUNCH WINDOW:	2015
ESTIMATED SALES:	$912 million

DRUG NAME:	IDegLira
COMPANY:	Novo Nordisk
PHASE:	III
ESTIMATED SALES:	$517 million

DRUG NAME:	omarigliptin
COMPANY:	Merck
PHASE:	III
LAUNCH WINDOW:	2017
ESTIMATED SALES:	$412 million

DRUG NAME:	brexpiprazole
COMPANY:	Otsuka/Lundbeck
PHASE:	Filed
LAUNCH WINDOW:	2016
ESTIMATED SALES:	$763 million

DRUG NAME:	ocrelizumab
COMPANY:	Genentech/ Roche
PHASE:	III
LAUNCH WINDOW:	2017
ESTIMATED SALES:	$355 million

DRUG NAME:	Zinbryta
COMPANY:	AbbVie/Biogen Idec
PHASE:	III
LAUNCH WINDOW:	2016
ESTIMATED SALES:	$320 million

DRUG NAME:	Plegridy
COMPANY:	Biogen Idec
PHASE:	Approved
ESTIMATED SALES:	$537 million

DRUG NAME:	Kalydeco/ lumacaftor
COMPANY:	Vertex
PHASE:	III
ESTIMATED SALES:	Blockbuster

DRUG NAME:	ALXN-1215
COMPANY:	Alexion
PHASE:	III
ESTIMATED SALES:	$578 million

DRUG NAME:	migalastat
COMPANY:	Amicus
PHASE:	III
ESTIMATED SALES:	$99 million

Also, there may be a little hope for patients with Huntington's disease. Early in the year, Raptor announced positive 18-month results on a three-year Phase II/III trial for RP103. In the study, total motor score progression was 32% slower in the RP103 group. An extended and delayed-release formulation of cysteamine bitartrate, RP103 recently received orphan drug designation from the European Commission. While it's still early in the process, good news is scant in Huntington's, so something to watch.

Rare diseases

Orphan disease therapies are becoming more and more popular with both big pharma and biotechs. The combination of exclusivity and a more streamlined path to market have made them increasingly appealing.

But while the orphan drug market has seen astronomical growth, there's been increasing push-back from payers over the prices for these medications. Given that cost containment is a central tenet of healthcare reform, it's unclear how six-figure prices will fare in the long run. To complicate the picture, patient advocacy groups have become increasingly engaged and will fight any measures that limit access. Given this environment, will payers balk at the growing slice of the pie going to specialty medications? No answers yet, but the implications are big.

At the top of the growing list of orphan drugs, Vertex may have a genuine blockbuster with its combination of lumacaftor and *Kalydeco* (ivacaftor) for cystic fibrosis. (CF) Recent Phase III results have been positive, though not overwhelming, showing the combo does improve lung function, just not as much as everyone would like.

Still, the drug has received FDA's breakthrough therapy designation and approval would dramatically increase the number of CF patients who could be treated with Vertex therapies. Right now, *Kalydeco* only helps around 4%, while the combination would cover around 50% of CF patients. Thomson Reuters puts the potential sales at $3.7 billion by 2019. Vertex is expected to file in the US and Europe by the end of the year.

Alexion acquired Enobia in 2012 and with it came asfotase alfa (ALXN-1215), which treats hypophosphatasia, an often deadly form of rickets. Alexion scooped up breakthrough therapy designation in 2013 for the enzyme replacement drug. A recently concluded study showed that five-year survival on the drug was 89%, compared to 27% for patients who received no treatment. The company submitted a rolling BLA in April. Thomson Reuters puts potential sales at $578 million by 2019.

There are a number of agents in the pipeline to treat Duchenne muscular dystrophy (DMD), which currently has few therapeutic options. One of these is *Translarna* (ataluren) from PTC. The small-molecule drug treats nonsense mutations in the dystrophin protein and was recently given conditional approval by the European Commission.

Prosensa's RNA drug drisapersen, an exon-skipping therapy, appears to be back from the dead. A Phase III study showed little advantage over placebo; however, additional data convinced the FDA to take another look. Drisapersen has breakthrough therapy status and the company is moving forward with an NDA.

Sarepta, which also takes an exon-skipping approach, is seeking early approval for its RNA drug eteplirsen, also for DMD. The company has experienced a bad combination of up and down trial results and corporate boardroom drama, but appears to be poised to submit the NDA for its DMD therapy. When approved, drisapersen and eteplirsen should be direct competitors.

Fabry disease is caused by mutations in the alpha-galactosidase A enzyme, which leads to fat build-up and a variety of painful and debilitating symptoms. There are a couple of approved Fabry treatments (*Fabrazyme* and *Replagal*), but they require weekly infusions that are especially difficult for children. However, Amicus has developed migalastat, a small-molecule drug that could help patients with less severe disease.

"One of the things people forget about enzyme-replacement therapies is that they require a significant amount of chair time," says Ritu Baral. "This has the potential to be a game changer in Fabry treatment because of its oral delivery."

Migalastat is designed to treat people who have some enzyme activity, as many as 50% of Fabry patients. The drug has had an up

and down path and GlaxoSmithKline pulled out of their deal with Amicus, but improved Phase III results have put the drug back on track. Thomson Reuters estimates sales at $99 million.

BioMarin has a promising therapy for Pompe disease, a lysosomal storage disorder that causes weakness and respiratory issues. BMN-701 has received FDA orphan drug designation and is in Phase III trials. Thomson Reuters puts potential sales at $163 million by 2019.

Stem cells

Stem cells have been long on potential but short on immediate benefit. However, that may be gradually changing, as a number of therapies are making their way through Phase III trials. Though it's difficult to gauge what kind of impact these therapeutics will have on health or markets, this might be the tip of the iceberg, and we will finally see some actual stem cell therapies make their way to patients.

While the majority of press has been devoted to the hand-wringing around embryonic stem cells and the blinding coolness of induced pluripotent stem cells, the therapies closest to market often rely on more differentiated cells. These treatments are a bit sparse on data and projections but they're interesting to watch and are likely a harbinger for bigger things to come.

One good example is *Revascor* (CEP-41750), Teva/Mesoblast's adult mesenchymal stem cell treatment for heart failure, which is currently in a large, 1,730-patient pivotal Phase III trial. Outcomes won't be available for some time but previous results have been encouraging, though they have come from small samples. While it won't be the blockbuster Novartis' LCZ-696 is expected to be, it could make a significant impact.

Gamida Cell is moving forward with its Phase III trial for *StemEx*, a therapy for blood cancers, such as leukemia and lymphoma. The therapy has orphan drug designation and fast track status and is intended for patients who cannot find a marrow donor. Gamida has been changing partners lately, with Teva dropping out and Novartis being an on-off-on suitor.

In earlier stages, both Stem Cells Inc. and Asterias are working on treatments for chronic spinal cord injuries, Asterias is picking up where Geron left off. In addition, there are a number of early-phase studies investigating the possibility of inhibiting cancer stem cells, which may provide a well of slow-growing cells that continuously reinvigorate certain tumors. Celgene has invested heavily in therapies that address cancer stem cells.

Odds and ends

As the year ends, Ebola is dominating the news and there's palpable hope that new treatments will rescue the world from a full-blown pandemic. Mapp, Sarepta, and Tekmira are collaborating with the World Health Organization, Wellcome Trust, and other organizations to begin trials in West Africa. In addition, OncoSynergy has received orphan drug designation for OS2966, which targets CD29 to treat glioblastoma and other aggressive cancers. But CD29 also plays a role in Ebola and the company is planning a trial.

Further out on the science frontier, Spark Therapeutic is in a Phase III for its ophthalmological gene therapy agent, which uses a viral vector to deliver the RPE65 gene to treat a number of eye conditions. This is a good candidate to be the first gene treatment approved in the US, but it certainly won't be the last. Gene therapy has risen quickly from being moribund to red hot.

Another area that's gaining ground is antibiotics. The Generating Antibiotic Incentives Now (GAIN) provisions are driving innovation in anti-bacterials in the same way the Orphan Drugs Act supported work on rare diseases. One interesting example is Cempra's solithromycin, which is in trials for community-acquired pneumonia and other infections. Thomson Reuters projects sales of $200 million by 2019.

Biosimilars are knocking on the door, but many questions remain about how they'll fare in the US market. Sandoz has filed a BLA for its version of *Neupogen*. Celltrion is right behind them with a biosimilar of *Remicade*. However, regulatory approval may be the easy part. Biosimilars still face patent battles, prospective price discounts remain hostage to the uncertainty around trial development costs, and there's no guarantee physicians will switch patients to these newer versions of established drugs.

And finally, far off on that distant horizon, there is keen interest in microbiota, the human body's friendly bacteria. Pfizer is partnering on drug candidates with Second Genome, a leader in this area, and there are a host of startup ventures coming out of the woodwork. This could be an interesting area for approval candidates in 2020.

Payer politics

As Gilead well knows from its *Sovaldi* experience, developing a groundbreaking therapy, and gaining FDA approval, doesn't guarantee blockbuster nirvana. Gilead has been a popular punching bag for *Sovaldi*'s perceived high price, but it is hardly unique. A number of emerging therapies are generating sticker shock, particularly in oncology.

How will payers push back? There's a lot of discussion—at conferences, in the media, in Congress—but no clear consensus has emerged. Some payers are already asking for evidence of value and there are potential trends towards referencing across borders and closed formularies. This will be a complicated societal issue, as drug companies, payers, and consumers wrestle with the question: How much is too much? PE

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Dane in America

Novo Nordisk's Jesper Hoiland.

By William Looney

Everyone knows that Novo Nordisk is a tightly focused enterprise neatly matched to a big disease footprint—diabetes, where it commands nearly 50% of the global insulin market. A critical—and less apparent—driver of the company's success has been its long journey to build a viable presence in the US, a market whose size and reach makes it a proving ground for any business with global aspirations. Prior to 2001, Novo Nordisk was just a bit player here, with annual sales below the $300 million mark. Paced by some risky investments to build a US sales force literally from scratch, the company raised that number tenfold in the years up to 2008, and then more than doubled it again after the introduction in 2009 of its breakthrough glucagon-like peptide-1 (GLP-1) analogue, *Victoza*. This year, Novo Nordisk's US sales are slated to surpass $7 billion, with *Victoza* alone racking up a 60%-plus share of the GLP-1 market.

To take a closer look at Novo Nordisk's blueprint for the US, *Pharm Exec* met last month with Senior Vice President for North America Jesper Hoiland. Hoiland, 54, a 27-year company veteran who assumed his post in August 2013, is the first native Dane to lead the US business. It's a distinction that Hoiland sees as an opportu-

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nity to create a broader cross-cultural perspective and promote better understanding of a complex—and often non-transparent—operating environment for medicines. In the following Q&A, Hoiland discusses his first year on the job at the company's regional headquarters in Princeton, including an unsettling initial encounter with the growing clout of pharmacy benefit manager (PBM) medicines gatekeepers; looming price wars; observations on the vital importance of stakeholder outreach in a transactional health system driven largely by relationships; all the advance planning required to unleash the promise of the eight to 10 new compounds Novo Nordisk hopes to commercialize by the end of the decade; and implementing what he sees as the three essential contributors to CEO leadership success: People. People—and People.

PE: *You joined Novo Nordisk in 1987. What was your first assignment? How have the company's clinical and business practices changed over the past 27 years?*

Hoiland: My first job as a young manager at Novo back in 1987 seems inconceivable today. The interesting part is that I was assigned to the US, at a time when we had virtually no presence here. Between Novo and Nordisk, which were still separate companies then, we had less than 75 people, including sales reps. Among other things, I was tasked to estimate the number of cattle Novo would need each year to fill the demand for human insulin, which was mostly extracted from cow glands. This depended, in turn, on accurate forecasts of the growth of the US diabetes market. Getting the right estimate was also important because in the 1980s the US dollar was highly volatile. All that seems fanciful now given the advances in both science and information.

Looking back over the years, our business practices have been affected most notably by information technology. In the 1980s, as the youngest manager on staff, I was good at adapting to the new data management tools coming on stream, which explains why I became the first person outside the finance department to be given a personal computer. I recall being asked by my supervisors to figure out what other uses Novo could find for it. Ironically, today I hardly use my desktop because I prefer to meet and talk to people directly. Personal interactions are the basis of my management style.

"Novo Nordisk has never been for sale … we are one of the few multinational companies operating on a 10-year planning cycle."

Not for sale

PE: *Further to business practices, hasn't Novo Nordisk's longstanding status as having a foundation as its majority shareholder kept it remarkably stable over the years, particularly compared to the short-term business pressures that confront publicly held enterprises?*

Hoiland: Our company history is unique. We began as two companies, Nordisk and Novo, founded in 1923 and 1925, respectively, led by Danish physician researchers and pharmacists with a passionate scientific interest in diabetes—a condition that, due to the discovery of the insulin hormone by two Canadian researchers, was then just emerging as a treatable chronic disease. The two new companies led the world in turning this discovery into a product with clinical—and commercial—applications. Ninety years later, and as a combined company since 1989, we are still the leader, not just in Europe, but globally. We are able to build on decades of work in progressing the treatment of diabetes, from the accessibility, safety, and stability of man-made insulin to innovations in therapeutic delivery devices as well as investments in diabetes control and prevention in diverse community settings—our products are now marketed in 180 countries.

The focus on diabetes was made possible by the decision of both companies to structure themselves as a foundation under Danish law, Nordisk in 1926 and Novo in 1951. This allowed profits to be plowed back into research and treatment activities rather than be subject to tax. Dr. Hans Christian Hagedorn, a co-founder of Nordisk and inventor of the first bulk manufacturing process for insulin derived from the bovine pancreas, put most of the company's early revenues into research, including founding the Steno Memorial Hospital, which exists to this day and has had a distinguished record over the years in treating more than half of the diabetic patients in Zeeland and Copenhagen. The Foundation was also the force behind our very early investments in the enzymes that trigger many metabolic processes, the understanding of which paved the way for the development of reliable, artificially derived sources of insulin. That sister company, Novozymes, is now the world's largest producer of enzymes for industrial and human uses; as with Novo Nordisk, the Foundation is the majority shareholder.

At present, more than 70% of votes are controlled by the Novo Nordisk Foundation. This gives management the ability to deflect two negative influences on proper business planning: M&A pressures driven by activist shareholders, whose only motive is scoring a run-up in the stock price; and financial reporting biased toward short-term quarterly results at the expense of long-term performance. Novo

Nordisk has never been for sale, even though over the years some prominent competitors have tried to buy us. We are one of the few multinational companies operating on a 10-year planning cycle.

Status as a foundation also colors the approach to corporate responsibility, where we adhere to "triple bottom line" reporting, which includes financial, social, and environmental performance metrics. We put that in place back in 2004, when we were the first major pharmaceutical company to do so. The commitment also shows in our record on executive compensation, where we have one of the lowest differential in this industry between our CEO's pay package and the pay of workers on the shop floor.

It pays to wander

PE: *Now that you are leading a transformed US organization for Novo Nordisk—it ranks today as the company's largest foreign operation—what lessons do you draw from that first assignment in the US market?*

Hoiland: My initial training in sales gave me basic knowledge about the pharmaceutical business that I continue to apply today. I still count as one of my proudest achievements the diploma I received after completing an arduous six-week course to obtain certification as a sales rep. I had to pass that test in order to keep my job. But that was only the beginning. Working in the field, meeting customers, and reacting spontaneously to their tough questions, convinced me that success does not come from sitting in an ivory tower.

Since I arrived as head of North America in August 2013, I've spent most of my time out of the office. I make an effort to visit and mingle with the sales force, whose numbers I have increased by nearly a fifth in the past year. I am reaching out to pharmacy benefit managers, payers, physicians, and nurses. I ask every diabetes patient I meet for their perspective on treatment. To the extent I can, I try to dialogue with regulators. I make it a point to be a guest lecturer at business schools, which I believe are a great source of ideas as well as giving me a chance to meet the next generation of managers. Because the US market is changing so quickly, it is important to possess a holistic, 360 degree view of what forces are shaping that change, especially because most of it is taking place outside our own narrow segment of the health system. To that end, this month, Houston became the first US city to join Novo Nordisk's "Cities Changing Diabetes," a global partnership focused on diabetes lifestyle education and fighting the rise in urban diabetes.

"When a company has multiple therapeutic area leads in each country, the country manager becomes little more than a concierge. … Matrix organizations ruin good companies."

PE: *What else about your background has helped in the transition to your current role?*

Hoiland: I've had extensive international exposure that gave me an inventory of best practices to spread through different country markets. Prior to my present position, I worked in various capacities in Canada, Belgium, France, and, finally, Australia, where I served as Novo Nordisk's General Manager. More recently, I've tackled strategy and coordination issues from HQ as head of Global Marketing as well as International Operations, which included P&L responsibility for country affiliates outside North America, Europe, and Japan. I spent upwards of 150 days a year traveling to more than 80 countries looking for organic market growth opportunities. It was my responsibility to share and translate what I learned with other affiliates. One principle I espoused during my international days: once Novo Nordisk makes a commitment to a country, we stay. We don't pull out. It can be hard to live up to this pledge. It has been more than difficult to keep our business going in Iraq. But we have.

Bad idea

PE: *What is your view of the matrix organizational model of managing a global business around multiple product lines or therapeutic areas?*

Hoiland: I lament the current fashion of downgrading the traditional country manager. When a company has multiple therapeutic area leads in each country, the country manager becomes little more than a concierge. This sows internal confusion, promotes conflict, and damages local reputation. How can a leader build effective relationships if you say one thing to staff and stakeholders, which can then be contradicted by another manager of equivalent status? Matrix organizations ruin good companies. We do not rely on the practice at Novo Nordisk; if we did, it would probably speed my path to retirement.

People make the product

PE: *Is there a "golden rule" that you apply to leading a business?*

Hoiland: Let me distill my basic philosophy into three principles. The first is the caliber of your people. I think human capital accounts for more than 50% of a company's success. The second is the image of the company. This reinforces the first principle, because a solid reputation attracts the best talent. The third principle rests on your products,

which in our industry is linked to quality and safety as well as clinical relevance and performance for patients. It's simple: finding the right people and putting them in positions where they can do the most good for the organization is the objective that every business leader should achieve first, above all others.

Another asset of this approach is that it avoids the tendency to "stovepipe" decision-making. It is important to be flexible about local cultures—there is always going to be a different way of doing things in Japan than in Denmark. However, I am also learning that there are more similarities among countries today that make it easier to manage the differences. It used to be said that the US and Europe followed entirely different models of healthcare, with contrasting roles for the government and the markets; businesses had no choice to adjust. Consider, however, that today in Denmark one fifth of the population has opted to take out private insurance to pay for their healthcare. Doesn't that remind you of the US? At the same time, the Affordable Care Act is likely to yield to more centralized decision-making under government supervision, which suggests there are learnings that can be transferred to the US from Europe.

Overall, in the next 10 years, I see a trend toward a merging of the models for the delivery and financing of healthcare, at least in the mature markets. The role of managers like me is to encourage that connectivity and share our distinct perspective in spreading best practices. For example, diabetes is on the front line of chronic disease—and Novo Nordisk knows precisely how to manage the challenge efficiently, in multiple care settings.

PE: *Having occupied the top line management position in North America for a little more than a year, what impressions do you have about the US pharmaceutical market?*

Hoiland: The US alone accounts for more than a third of the global market for pharmaceuticals. No company with global aspirations can afford not to be active and engaged here. Up until the year 2000, Novo Nordisk was squarely in the position of aspirant; we reversed it through a combination of tenacity and focus that relied heavily on the talent of our people.

"What you have in the US is an elaborate, negotiated system of drug rebates calibrated on the negotiating circumstances of each party."

Many experts say the US market is unique. This is true, to an extent. The employer-paid insurance model is different. But the claim the US has "price elasticity" in the form of flexible free pricing is accurate only for the relatively small specialty/orphan drug segment. The reality is list prices don't reflect what is really happening in negotiations, where the net take-home price ends up being very different. And such negotiations are usually conducted in a manner that is not transparent. To make the point in lay terms, I cite the analogy of the price for a hotel room you see on the door after you check in. If you paid $250 at registration compared to the $500 posted in the room, you think that's a wonderful bargain. But even that price is not reflective of reality: if by chance you are a frequent guest of the hotel, then your price will be another 20% lower, or $200. Then there are the last-minute buyers with no reservation for a hotel room for the evening. If the room is still unreserved at noon time, then there will be a middle-man with a smart phone app that will be able to sell it to you for $100.

So is this $500 list price the actual cost for reserving the room for the night? Certainly not. What you have in the US is an elaborate, negotiated system of drug rebates calibrated on the negotiating circumstances of each party. Steep discounts from drugmakers are expected and built in to the system. Right now, you can say the process is not very clear or open and tends to reflect the unacknowledged preferences of the payer. But that is going to change in the next five years due to a combination of powerful new information processing technologies, government disclosure, and compliance mandates, as well as structural changes like the consolidation of purchaser and provider services and disincentives around fee-for-service. Patient power will be important, too, because as patients pay more out of pocket, their sensitivity to costs will increase.

PE: *How are these market drivers shaping your strategic agenda for the US business?*

Hoiland: The biggest response so far lies in the restructure of our US sales force. My first decision was to create a new setup that acknowledges the traditional rep/physician contact alone will not push our business forward. In anticipation of new products, we have significantly increased our numbers of reps, while at the same time training and directing them differently, to focus less on direct selling than providing interpretive analytics, logistics, and data retrieval services. Despite all the benefits of this new technology, I am also still convinced that "boots on the ground" makes a difference because

of the vast differences you see on a geographic basis in the US; it's not a homogenous market, so you need reps who can accurately interpret the territory. We've added 350 reps to the sales force in the last year, precisely for that reason.

Of course, we are also making big investments to keep pace with the decision-making chain around access. Today, physicians are only one element in the customer base for our medicines, and their influence is declining. Instead, you have the federal government, through Medicare, Medicaid, the VA, and the DOD, plus employers, PBMs, and the new ACO model, as well as patient out of pocket. Every one of these stakeholders—I've identified up to 10—requires a distinct approach. I am involved in direct interface with each of them.

Specifically, we are addressing proactively the provisions of the Affordable Care Act to determine how our medicines can be better utilized in the battle against chronic conditions, which is the top category of health spending—yet the complexity of co-pay provisions in the law means that, for the average patient, drug coverage is less than optimal in managing their condition uninterrupted, for the long-term. We also see how high co-insurance rates are a burden for patients, even those of middle-income status; many in this group are effectively under-insured, which hurt access to our medicines.

Formulary fracas

PE: *Payer consolidation allows PBMs to leverage formulary controls to limit access to therapies. Use of this "nuclear option" is growing. Specifically, how did you respond to the removal last year of your top products, Victoza and Novolog, from the Express Scripts list of formulary-approved medicines?*

Hoiland: The decision was taken prior to my arrival in the US; there was no opportunity to walk it back. Obviously, we disagree with the action, especially the premise behind it. It has put a dent in US sales of *Victoza*, but we have recouped some share due to stepped up efforts to highlight the strong clinical profile of *Victoza* against all competing GLP-1 agonists—including the two products that replaced *Victoza* on the Express Scripts approved list—as well as its value in improving overall health outcomes for patients on therapy.

"Personally, I wonder how much Express Scripts has benefited financially from the decision, as patients switch to less familiar alternatives [to Victoza]."

Our strategy going forward has been clear and unequivocal: we are not seeking a formulary relisting based on any price acceptable to Express Scripts. We believe we have a high quality medicine, the denial of access to which is bad for patients. Our contacts with the physician community reveal a large number of *Victoza* prescribers would have preferred a different result, a perspective we have shared with Express Scripts and other stakeholders. Personally, I wonder how much Express Scripts has benefited financially from the decision, as patients switch to less familiar alternatives. And our competitors have clearly had to expand their use of rebating in addition to obtaining their current approved position on the drug list.

PE: *So Novo Nordisk does not intend to pursue, as others have done, reinstatement by conceding on price?*

Hoiland: We prefer a different approach, one based on our clinical performance that has in turn increased Novo Nordisk's market capitalization to a level higher than many other big pharma players. We are aggressively defending our pricing as justifiable in the context of our products' overall clinical and economic value, to providers and patients. One action I am taking directly is to strengthen our outreach and relationships to cover all corners of the marketplace, to ensure this abrupt impasse with Express Scripts does not happen again. What we have now is, in my opinion, a "lose-lose" situation, when in fact there was always the potential for a "win-win," had we been able to build in more dialogue. True, it requires a lot of tenacity and persistence—but like anything worthwhile in life, it usually takes five no's to get to a yes.

Trumping with Tresiba

PE: *You have the opportunity to set this stakeholder engagement approach in motion with a prospective FDA approval next year of your next generation, long-acting insulin, Tresiba, already in use in Europe.*

Hoiland: We are confident that we can present a strong case for *Tresiba* as clinically superior to the current standard of care in diabetes control. Access to any breakthrough justifies some form of premium on price. Of course, that price is open to negotiation—and should be. But given the billion-dollar costs of new drug development, if you end up essentially giving your product away, then the result is an industry that will not survive as the main source of the next generation of innovations.

PE: *How do patients figure in this equation?*

Hoiland: The bottom line for all patients is having access to a useful medicine. There are many tactics we can use to achieve that, includ-

Photo: Thinkstock

ing the appropriate use of coupons and co-pay offsets. It is important that patients remain aware of the clinical differences among products in the same therapeutic class, and to have the option to continue with a drug that has treated their condition successfully. Offsets allow for a choice—and choice is very important to the patient mindset. In Denmark, we have a process where a maximum reimbursement is set for a medicine based on a detailed examination of health economics data. If the price is higher than this amount, the patient is responsible for the balance. And there is insurance available to help the patient to do just that. This is one of the more sensible approaches to creating more options for the patient. I sense it is a trend that will spread to other countries, including the US.

PE: *Novo Nordisk has had some highly successful new product launches in the past few years. How do you assess the current launch environment in the US—are you meeting initial expectations with the new Levemir FlexTouch pen device?*

Hoiland: We launched FlexTouch here on June 24. It represents a new, accurate, and accessible way for patients to administer their insulin. It's already a huge success in Canada and early figures here look very convincing. A strong start is important: in the old days, nine months of sales were required to assess a launch success; today, the verdict is in at six weeks. The device has had good feedback from patients and especially from physicians, whom we have been cultivating with great care and commitment ever since we introduced to the world our first pen device for insulin, NovoPen, back in 1986.

Insulin devices exemplify how difficult it can be to obtain market acceptance for a genuine innovation. That first NovoPen device experienced early acceptance everywhere except the US. The device represented an advance in the level of convenience for insulin patients, yet, surprisingly, in the world's most consumer oriented market, we were unable to fight reliance on the traditional vial and syringe. Why? Because we lacked inroads to the pharmacy practice: our small team of sales reps might garner "wows" from physicians but when we persuaded them to write prescriptions for the pen, pharmacists would simply substitute it with that vial and syringe. It was a product they were familiar with—and because there

were some extra processes involved, they got paid more for it.

So we had to work very hard, over several decades, to overcome that resistance, largely by continuing to build on the pen concept to create products with such a formidable array of patient benefits the resistance disappeared. Our latest launch represents our fifth generation of durable pen devices, which can now store as many as 80 units of insulin in one convenient, long-use device. That's a doubling of our previous limit of 40 units. It represents a major advance in innovation for patients who need more than those 40 units—more than half of the US diabetic population.

Disruptive threats

PE: *Innovation can also be disruptive and threaten established enterprises that lose the capacity to anticipate market change. Have you considered what "shot out of the blue" might pose a serious threat to Novo Nordisk's leadership in diabetes?*

Hoiland: We've been in this business for 90 years. We have demonstrated the capacity to adapt, over and over. Certainly we have to keep pace with scientific progress, particularly in areas like stem cells that can restore the ability of the pancreas to produce insulin. Researchers always say that we are ten years away from reaping the promise of stem cell research. However, Novo Nordisk is actively studying this area, and we are prepared to seize any clinical or commercial opportunities that lead from it. The other potential disruption is some change that attacks diabetes at its root, in terms of wellness, prevention, and lifestyle. Human nature is a formidable opponent—there is an innate tendency for us to eat more, to crave bad things, and to exercise less. Hence, if someone discovered a way to fight fat and get lean and mean with no effort expended, it might force us to shift from the current diabetes treatment model focused on insulin replacement. It will be interesting to see if recent research pointing to a relationship between artificial sweeteners and the metabolic syndrome that leads to type 2 diabetes will spur a reduction in their use—will people start drinking water again? Assuming you could find that magic bullet on lifestyle adjustment, I still think the biggest impact would be on adjacent businesses like food, organized sports, and entertainment. At present, there is little on the horizon to stop the inexorable rise in the incidence of diabetes. We expect that the number of diabetics in the US — presently at 29 million—will surpass 10% of the population within the next two years.

"We expect that the number of diabetics in the US—presently at 29 million—will surpass 10% of the population within the next two years."

PE: *What about the potential of inhalable insulin delivery?*

Hoiland: There should be safe alternatives to injection, but ultimately the market and the patient community will decide its commercial potential. Needle phobia has been oversold as an issue in compliance; the bigger challenge was the stigma associated with the daily requirement to inject, but much of that has disappeared in the last two decades due to the consumer appeal of all these fancy new pen devices.

The test: Keeping patients happy

PE: *As a final thought, how do you define success in your role leading North America two or three years from now?*

Hoiland: The critical objective for me is to be able to say that, through our collective efforts, patients here in the US and Canada are being diagnosed early and are managing their condition well to achieve better glycemic control and good health. I am always asked about the competition: to be blunt, I don't care about our rivals for market share. They are mostly good products; I can't do much about them. My focus has to stay on what we do to make a difference to patients with diabetes—that's something I can influence. FDA approval and a strong launch for *Tresiba* will be critical to realizing this vision. And we are resolved to extend this commitment beyond diabetes, especially in adjacent product segments that include obesity, hormonal treatments, and blood disorders like haemophilia, where, like diabetes, we are a long-standing market leader. All told, we are working on eight to 10 new compounds in our core therapy areas that we hope to commercialize by the end of this decade. The US is going to be crucial to this effort.

In particular, the US will be a test of evolving approaches to treating obesity as a stand-alone condition. We passed a key hurdle with September's near-unanimous endorsement by a FDA advisory committee of *Saxenda*, our once-daily human GLP-1 analogue, as a new treatment for certain people with obesity. Assuming it is approved, this drug will require all of our stakeholder outreach skills to ensure its success. Obesity may be endemic in this country, but to many outside the medical profession it remains a social stigma associated with a lack of personal self-control. We as a society—not just us in industry—must work harder to place this condition in its proper clinical context. PE

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Photo: Thinkstock

'The Devil Beyond the Detailing:'

Sales reps and the new commercial organization

Structural transformations in the life sciences industry have put the traditional sales role under increasing scrutiny, with the most prominent change being a drastic reduction in field force deployments in the US and Europe. This, argues Hay Group's Ian Wilcox, is where opportunity lies. By rethinking the role of the sales rep and the new skills it demands—and then executing boldly around a new customer-driven master plan—pharma companies can put themselves in a prime competitive position.

By Ian Wilcox

Among all the changes that the commercial side of the pharmaceutical industry has undergone in the last decade, the most impactful has been the redistribution of customer influence. There's been a shift away from individual physicians and towards payers (as well as medical institutions and patients). The result of this change? The roles of the sales rep and the commercial organization behind it need to change—and not just incrementally.

Today's customers focus on value. This certainly includes the most time-honored sales factor—therapeutic efficacy. But today, cost issues have become more prominent and problematic—complicated by different customer needs and different socioeconomic factors. And beyond this, customers are looking for value that extends beyond straight measures of efficacy or cost—extending to ancillary services that may benefit patients, providers, and payers alike. Examples include

resources that make sure patients take the right dosage of their medication, or online tools for medical professionals that are effective and user-friendly—or, better yet, innovative.

The classic rep activity of "detailing" a specific product's benefits to customers is now almost an artifact of a previous era. This information is available in other ways and there are other important factors to emphasize in the new value proposition.

A direction without a roadmap

While there's general agreement on the issues pharma companies face, many executives still aren't clear (or decisive) about how to improve their commercial organizations or the role of the sales rep.

That said, there certainly have been discussions and experiments. For instance, organizations have added required competencies like resilience to the existing rep role—not a bad thought, but not a bold move either.

Other well-intentioned tactics include:

- **"Delinking" sales force compensation** from sales volume.
- **Moving from the usual "regional sales manager"** model to an "account manager" model that expands the individual rep role.
- **Aggressively leveraging technology**—for instance, through so-called e-detailing or Skype sessions or by transitioning the focus of the role to more of an "information broker."
- Even **establishing a lower-level rep role** that focuses on dropping samples and keeping contact, while reserving significant interaction for a higher-level rep/team with sophisticated medical knowledge and strategic focus.

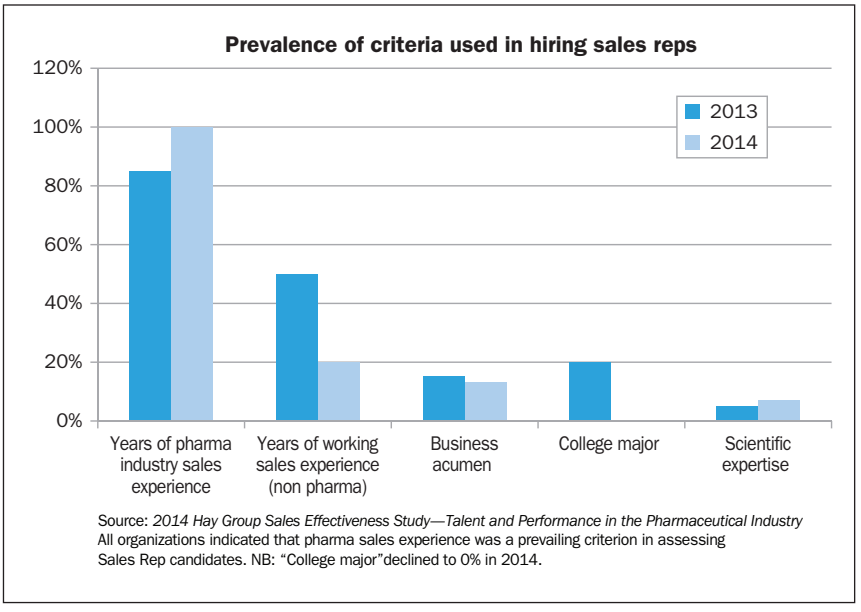
But in many cases, these kinds of changes just aren't far-reaching enough. They may not be staffed for success. Or, they're moving too slowly (see sidebar on page 39).

Pursuing the service model

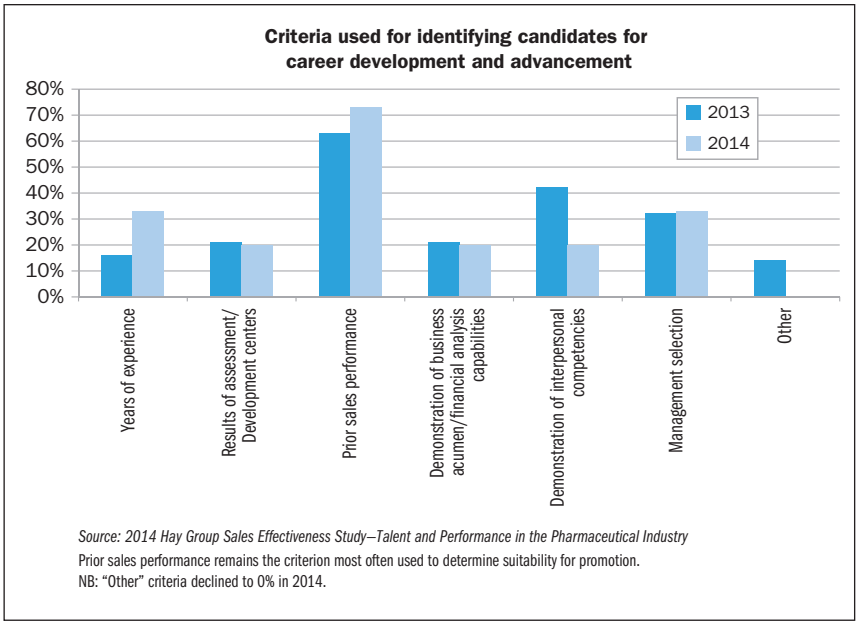
The rep role that previously focused on exerting influence and providing guidance is now becoming a service model. This means the rep acts as a conduit to help physicians and related customers access information and resources.

In a March 2014 profile in *Pharm Exec*, Dr. David Nash, Dean of the Jefferson Medical University School of Population Health, said "The most disruptive action a pharma company can take is to trump the competition with new and more effective tools to educate the patient. It's very simple: the most sensible investment is one which will contribute to making patients better consumers of medicine."

Back up the commercial organization chain, anecdotal evidence suggests that managers are becoming less focused on "pull through" (numbers of prescriptions) and are managing the business relationship with pharmaco-economic data. When doing this, they use analytical tools to help payers/institutions see how a portfolio of products benefits them.



Source: *2014 Hay Group Sales Effectiveness Study—Talent and Performance in the Pharmaceutical Industry*
All organizations indicated that pharma sales experience was a prevailing criterion in assessing Sales Rep candidates. NB: "College major"declined to 0% in 2014.



Source: 2014 Hay Group Sales Effectiveness Study—Talent and Performance in the Pharmaceutical Industry
Prior sales performance remains the criterion most often used to determine suitability for promotion.
NB: "Other" criteria declined to 0% in 2014.

Most prevalent 'primary' performance measures to determine incentive payout

Criterion	General Physician Rep	Specialist Physician Rep	Hospital Rep	Corporate/ National Accounts	Regional Accounts
Scrips/Units	100%	90%	80%	67%	80%
Market Share	75%	30%	50%	20%	25%
MBO/Special Projects	–	25%	33%	56%	50%
Compliance	–	33%	33%	20%	25%

Source: 2014 Hay Group Sales Effectiveness Study—Compensation Policies and Practices in the Pharmaceutical Industry

Life sciences companies do not appear to be "incentivizing" their sales reps and account managers in a way that indicates a changing approach to their markets. The most prevalent primary criteria across all employee groups for determining incentive payout remain scripts/units.

Your 'To-Do' list for the commercial organization and people in sales

Building an effective response to these strategic challenges requires a clear plan and laser-like focus that starts with the assertion that success depends ultimately on the way management communicates with this valuable storehouse of human capital.

The commercial organization. The commercial organization for 2014 and beyond must:

Customers are looking for value that extends beyond straight measures of efficacy or cost—extending to ancillary services that may benefit patients, providers, and payers alike.

- Connect with customers (through all your services) to make sure you know what they value.
- Make sure everyone in your company knows what your customers value (and that they all agree on it).
- Focus more on your key accounts than geography.
- Arm your sales force with a clear, attractive value proposition that can be communicated at all levels—describing what you offer, in both your products and related services.
- Find ways to open sustainable communications channels, so that you can keep up to date with what your customers want. Work closely with other parts of the organization—especially R&D, R&D partners, and market access teams.

The people in sales. A successful new commercial organization will need people with skills that current reps may not possess. These people are no longer just reps in the classic sense. They provide a conduit of sorts for physicians and other healthcare providers to gain access to resources and tools within their companies' networks. So, what qualities should the core people in sales possess?

- A strong medical science background, so they can understand and communicate sophisticated and complex information about advanced therapies.
- Outstanding relationship building skills, but more on an institutional level than the interpersonal level that has characterized the traditional rep.
- The ability to adapt to changing situations and provide different levels of discourse and service depending on the audience.
- A strategic orientation that enables them to confront issues and find solutions at a higher level.
- A level of technical knowledge and understanding that will allow them to team with technical professionals to provide solutions (as opposed to handing them off).

A key factor here is to re-assess current reps for their suitability to this new role. Their previous success working under an old model (likely with performance measures that no longer fit the new role) is no guarantee of future success. Not all will have the new skills, behavioral characteristics, or motivation to be able to develop them quickly enough.

Getting moving: Some things to think about

Companies that rethink the commercial organization correctly in the context of a good understanding of relevant market dynamics and then move the fastest to apply this to the revamped rep role will have the competitive edge.

What you should do. To help you work out what you should do, there are some basic steps and questions to consider:

- Determine the true level of commitment within your organization to this kind of meaningful change.
- Think about the changes in your commercial organization from the years before the economic crisis of 2008-2009 through to today. Which changes would you classify as stopgap and which would you classify as forward thinking?
- Which of those stopgap measures (perhaps cuts or re-organization or re-distribution of people) have been re-visited and how?

» What effect did the more progressive or experimental changes have?
» Where changes weren't successful, what were the reasons? Cultural resistance? Lack of clarity? Not enough people or money? Or were they poorly thought through?
» For those changes with potential, how could they be adapted?
» Consider the pros and cons of each change.

Once you've found a scenario that you think would work, ask yourself whether you have enough of the right people to follow through on it and how you might obtain appropriate resources if you come up short.

Tinkering with the structure of the commercial organization or the competency profiles for the sales rep role isn't enough.

Also consider the following:

» The work proposition for 2014 and beyond—what might the career track look like for members of the new commercial organization, particularly reps?
» Where will you find your talent?—and should you look internally beyond your own commercial organization and externally outside the pharma industry (or even outside of people with sales/marketing experience)?
» Performance measures—what traditional measures make sense and, almost as importantly, what metrics no longer make sense?
» Reward—how will roles calling for a new—often higher-level—set of talents be priced in the marketplace? And what might the total remuneration implications be?

Data Reveal More Sales Rep *Status Quo* than Sales Rep Revolution

Has the rep model suggested here been embraced by the industry? Latest data from companies in our 2014 Hay Group studies—Talent & Performance in the Pharmaceutical Industry, Market Access and Emerging Commercial Practices, and Compensation Policies and Practices in the Pharmaceutical Industry—show that little has changed. Nonetheless, most companies are at least trying to get farther on the journey to a customer-and-consumer focused sales model over the next two to three years.

A distillation of key findings from this research indicates the following:

- No organization in our surveys wants to be solely sales-focused two to three years from now.
- 45% want to be customer-and-consumer focused two to three years from now.
- There's a recognition of payers' growing importance. While 10% of respondents say they deem health economics knowledge—knowledge that appeals to payer interest in metrics linked to broad outcomes—an important capacity for account managers, 20% say it will be important a year from now.
- These numbers show strong desire to change. But actions don't match aspirations. Current practices are out of line with the goal to achieve a customer-and-consumer focus:
- 60% of companies hire account managers from existing sales force. Predictably, the figure suggests that a sales mentality still dominates.
- 53% of companies don't have a job rotation program for reps. The number reveals that a commitment to cross-functional thinking hasn't taken hold, that the rep profile remains heavily sales-skill focused.

It's a shame that companies aren't making more progress, because it looks like the next few years will bring real opportunity to improve. There's more churn predicted for the near future, turnover that's an opportunity to rethink the sales role.

- Companies are reporting more vacancies (3.5% vs. 6.7% from 2013 to 2014).
- Predicted voluntary turnover is higher this year. For example, in 2014, 38% of companies surveyed predict turnover among national account managers, compared to 7% last year.

The bottom line: Companies in biopharmaceuticals have the desire to change. The question is whether they have the will.

Fundamental, disruptive changes in the industry require nothing less than a true mindset change. The core commercial organization and its sales rep engine are certainly at the center of any new mindset. But lasting impact—especially in this mission critical area of sales —means:

» Getting genuine **commitment** from top management to proceed with the plan.
» Assembling a team with the **change management competencies** to move forward.
» Producing a **comprehensive analysis** of your organization's strategic and tactical issues around its commercial function—and its relation to other parts of the organization.
» Creating an internal **consensus** on what needs to be done, and then incorporating this into a "do-able" blueprint for action.

Tinkering with the structure of the commercial organization or the competency profiles for the sales rep role isn't enough. Game-changing events on the life sciences landscape demand game-changing action from the life sciences industry at its critical point of customer contact: the sales representative. PE

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Digital's Place in the Pharma Marketing Mix

The rush to digital will continue at a fast clip, but marketers need to reacquaint themselves with their brands' audiences.

Thirty-nine years ago this past June, an article appeared in *BusinessWeek* that offered readers what was for its time a startling degree of foresight. Four paragraphs down, just above their first historic mention of what they called "the paperless office," the authors of "The Office of the Future" passed along a prediction by George Pake, head of Xerox's Palo Alto Research Center:

"Pake says that in 1995 his office will be completely different; there will be a TV-display terminal with keyboard sitting on his desk. 'I'll be able to call up documents from my files on the screen, or by pressing a button,' he says. 'I can get my mail or any messages. I don't know how much hard copy [printed paper] I'll want in this world.'"

Coming in a time when the typewriter was still *de rigueur* in any modern office, the first part of Pake's prediction was far-seeing—and quite correct. The integration of computers into office environments may seem like a self-evident development with hindsight—but I don't recall anyone predicting the future ubiquity of smartphones or social media 20 years ago. So the first part of Pake's prediction should be considered one of the more impressive in the history of business prophecy.

The second part of Pake's prediction—the bit about paper—is more troublesome. In the same 20 years that saw Pake's display terminal prediction come true, the use of paper in North American offices actually rose. And while paper use in offices has declined somewhat since the 1990s, overall world consumption of paper has grown by four times since Pake made his prediction.

Why the history lesson? Because we as marketers need to get out of our heads the idea that the advent of digital technologies means the immediate irrelevance of more traditional forms of communication.

Why? Because in today's world, the speed of technology evolution is outpacing human habits, and human nature. People have been reading and writing and sketching on paper for nearly two thousand years, and on a variety of other non-digital tactile media for unknown thousands of years before that. We'll probably reach the age of the paperless office and fully paperless content consumption someday, but it'll most likely be after everyone who reads this article is dead.

Any evolution in the fundamentals of ways humans communicate and perceive their world takes a long time—generations steeped in the old ways must pass and new generations be born, often several times over, before such an evolution can be considered complete. Even evolution itself is an evolution—"On the Origin of Species" was first published more than 150 years ago, and still only about six in ten Americans—or so says Pew Research—believe in its fundamental assertion.

According to the AMA's Physician Master File, 47.4% of all active physicians were age 50 and up as of 2012. So nearly half of our single most important constituency are old enough to remember watching the Apollo 11 mission on television. Also, more than half of physicians regardless of age—55%, according to Kantar's latest survey—still read articles from medical publications in physical form, nearly double the number who read such articles on a tablet and well more

Yes, digital is the future of marketing. But brands and the people that use them don't live in the future—they live now.

Evolution, not revolution

We as marketers can achieve extraordinary things with digital tools. They have transformed the business of health, greatly for the better, and will continue to do so in ways that we can barely imagine today.

But no matter how enthusiastic we are about the shiny new tools in our toolbox, and no matter how much we talk to each other at digital conferences about how digital and mobile and social have grown from mere tactics to Capital-S Strategy, vast swaths of our audience are still consuming vast swaths of content via traditional channels.

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than double the number that read them on a smartphone.

Patients too. While the median age of the American population is 37, the use of healthcare isn't distributed evenly across that population. According to one published study, only a fifth of the average person's lifetime medical expenditure will be spent during the first half of his/her life, and nearly half of that expenditure will occur after age 65. That's not to say that young people don't consume plenty of healthcare services—of course they do. But older people consume a lot more. And in ten years, older people will still consume a lot more, and those older people will still be old enough to have begun their professional lives well before the advent of the desktop computer, let alone the smartphone or tablet or social media. These are people whose formative years were spent consuming information via traditional, non-digital means, and a large number of them still prefer to consume information that way.

Back to basics

All this being the case, when considering the proper place of digital media in any marketing mix, we need to go back to basics. The question for marketers is the same today as it was in 1914 and will be in 2114: Who is our audience, and what is the best way to communicate with that audience? Now, brand audiences are not monolithic—they include all sorts of internal variations depending on the variables of each brand's labeling and value proposition, not to mention the variability of people and their information consumption habits. That's why one needs a marketing mix. But if we really know our audience, we can at least draw certain basic conclusions. Such as: if our median audience member is more than 50 years old, it would be foolish for the center of gravity of our marketing mix to lie on the digital side of the scale.

Photo: Thinkstock

So why the rush to digital? We as marketers are suffering from a cognitive bias—a bias in favor of our own preferences. We are by nature creative and innovative people, and it's our responsibility to stay abreast of new developments in marketing, so we surround ourselves with the new, the innovative, the transformative. Digital turns us on. So we have a tendency to place our audiences in our shoes, rather than the reverse. We see our audience not as they are, but as we are. In so doing, we run the risk of failing to place our messaging in front of large numbers of people who might well benefit from it, people who don't correspond to our own biases about media consumption.

To avoid the effects of this cognitive bias, we need to reacquaint ourselves with our brands' audiences. The emergence of digital media and research tools offers us greater capacity than we've ever had before to find out as much as possible about our audiences' individual content delivery preferences. Then, we can go about the task of defining—or redefining—our marketing mix, incorporating digital and traditional elements as the audience's nature dictates. That mix will likely include a majority of one and a significant minority of the other, depending on the nature of the audience. But it will always be a mix, strategically appropriate content passing through a carefully balanced recipe of the various forms of media delivery, digital and otherwise.

Yes, digital is the future of marketing. But brands and the people that use them don't live in the future— they live now. To be successful as marketers, we need to remember two things: 1) that our messages belong where our audience is today—not where they may be in the future and 2) because our target audiences are not homogeneous, applying a balanced marketing mix is crucial. Whether the medium is stone, papyrus, paper, billboards, bus stops, television, desktops, smartphones, the Oculus Rift, or little chips embedded in the brain—wherever our audience is today, in all its infinite variations, that's where our message belongs. PE

Voices from the Community

TAG touts progress in global access to TB drugs.

Tuberculosis (TB) advocacy campaigner Treatment Action Group (TAG) has reached a milestone in improving access to TB treatments. The efforts of the research and policy think tank were fruitful as Sanofi reduced the 340B federal discount program price of *Priftin* (rifapentine) from $73 to $51 and further in January to $32 per box, according to TAG's website. The collective action resulted in a historical win for the TB community with a 57% reduction in *Priftin*'s cost, says Erica Lessem, TB/HIV project assistant director. And in spite of the aggressive stance taken by TAG, including two open letters to Sanofi and pressure by way of the #shameSanofi twitter countdown, the Paris-based drug company is today "more committed than ever to TB treatments."

"TAG vows to do more than just get in the room" to drive drug development for TB elimination, says Colleen Daniels, TB/HIV project director. TAG wants to be certain, she says, that its presence isn't merely a box for drugmakers to check, but a signal for meaningful engagement around a patient-centered approach.

Using similar bold and direct tactics for *Sirturo* (bedaquiline), TAG and a TB coalition sent an open letter to Janssen in September appealing for a reduction in the drug's price for all non-high-income countries as well as a meeting with the company, policymakers, and key funders of TB drug procurement. Janssen has indicated interest in negotiating on the price of *Sirturo*, says Lessem. TAG has been involved in the design of the next set of *Sirturo*'s studies and has pushed Janssen to assure trials that are rigorous scientifically and ethically, she notes.

In contrast to the collaboration between TAG and Janssen, Japan's Otsuka has taken a more closed-door approach to working with the think tank. Lessem says the lack of openness and responsiveness to the TB advocacy community is an indicator of a less rigorous trial protocol, and ultimately, the result has been less success with regulatory agencies for Otsuka's *Deltyba* (delamanid), which only has approvals in Europe and Japan so far.

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Roots in HIV

TAG's roots date back to the early era of AIDS activism. In 1992, several members of the Treatment and Data Committee of ACT UP (the AIDS Coalition to Unleash Power) left to establish TAG, to push for clinical trials and evidence-based approval of HIV drugs. Now the science-based think tank divides its efforts across HIV, and its deadliest co-infections, TB and hepatitis C, according to Daniels.

There are around two billion people with latent TB infection, and we need to be able to prevent them from developing active TB, which kills around 1.5 million people a year, says Daniels. There are not enough efforts in pharma working on preventing TB activation, especially for those possibly infected with drug-resistant strains of the disease.

In endemic areas like South Africa with simultaneously high rates of TB and HIV, patients take drugs that have been in use for 60 years. The drugs have major toxicity and tolerability issues and must be taken in sequence under close supervision; stopping the drug results in loss of the treatment's effect, Daniels explains.

We need drugs that can be taken for shorter duration with better tolerance and adherence, but there are few prospects for improved therapies, she says.

The drug development process in TB is "absolutely broken," adds Lessem. "The incentives for R&D are all in the wrong way so that it's not actually about getting drugs into patients. Its about making money in the big markets," she says. "There are few companies actually investing in TB research, and we've actually seen, recently, that Pfizer and AstraZeneca have pulled out." Last year, TAG reported the first decline in global funding for TB research since the organization began tracking numbers in 2005. This decline was driven primarily by pharmaceutical companies abandoning TB research. With total investments under $100 million, private sector companies spent less on TB research in 2013 than they did in 2009, at the peak of the economic crisis. Many in the TB community are pessimistic when talking about controlling the disease. "We want to change the discourse in TB so that we coalesce around a vision," says Daniels. "We can get to TB elimination."

HIV pre-exposure prophylaxis

TAG works globally but has a domestic focus working with minority populations on drug pricing and access in the context of the Affordable Care Act and different state exchanges. The organization looks at how structural and social factors prevent treatment and care from being implemented effectively in the US, notes Jeremiah Johnson, HIV prevention research and policy coordinator for TAG.

A major topic the group has confronted has been pre-exposure prophylaxis (PrEP), says Johnson. A big problem is that those who would most benefit from PrEP still need greater access to accurate information about their risks for acquiring the virus as well as all of their options for avoiding seroconversion.

Truvada from Gilead has hit a political "minefield," says Johnson. "I think there is some interest in the market," he notes. "But it's hard to gauge what Gilead's real perspective is. The community isn't completely behind pre-exposure prophylaxis and there are fears around reducing condom use, and questions around how the therapy works with existing prevention efforts."

Gilead has been willing to help sponsor community organizations to create their own PrEP campaigns, but lately is taking a more hands-off approach, says Johnson. PE

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