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VOLUME 34, NUMBER 6
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The Next List

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THIS MONTH'S TOP FEATURE is our annual review of who tops the league in industry sales—a standard benchmark of success that has remained surprisingly static since we began ranking the 50 largest players back in our April 2000 issue. Over these 14 years, just three companies—Merck (in 2000), Pfizer (from 2001 to 2013), and Novartis (this year) —have snagged the No. 1 position. Much of the real action has taken place well below the top, particularly among those middle-ranked companies which have achieved the scale to compete globally but where size has not yet proved a distraction against the bottom line.

As befits a publication with deep roots, *Pharm Exec*'s Top 50 has been around enough to reveal the importance of leading with a unique business model and then sticking with it, for the long-term. Two obscure entries on that first April 2000 list were Genentech (at No. 42) and Teva (at 43). By 2007, at the halfway point in the history of our survey, both companies had risen to a position in the top 20, paced by their achievements in securing dominant positions in the innovative cancer and generic segments, respectively. Teva—now twelfth in this year's list—will likely strike the top 10 next year, while the absorption of Genentech by Roche in 2009 has had much to do with its parent's own rapid rise from eighth place that year, to third.

What we are seeing now is a similarly decisive distinction favoring companies that made an early commitment to focus on specialty biologics for hard-to-treat conditions affecting small target populations. It's only a matter of time before these outliers—like Celgene (at 26 this year), Biogen Idec (27) and Shire (32)—breach that top 20 barrier, too.

Still, it is pertinent to ask whether such rankings remain the best way to document true leadership in the industry. *Pharm Exec* is a media enterprise and like everyone we face pressures to communicate in short, easy information bits; lists do serve a purpose in distilling complexity into a stimulating, commemorative tonic. But their shelf life is brief. In fact, the strategy dialogue within biopharmaceuticals today has shifted from celebrating bigness and scale—organizational attributes deemed critical to finding that "blue ocean space" beyond the reach of competitors—to embracing the concept of "fleetness," where the ability to make rapid, turn-on-a-dime decisions is essential to keeping pace with a business environment in perpetual motion.

According to Columbia Business School Professor Rita McGrath, "If you think of competitive advantage today as something temporary or transient, you'll organize your company in a very different way. And you will re-do it often." In other words, in this world, size can be a drag. Foresight is a lot harder when you are at the top, looking down, not out. And few executives want to confront the trade-offs from being aware that the biggest threats to the business might be in adjacent industries and sectors: that is, beyond the Pharma 50, not within it.

The dismembering of competitive advantage is so dramatic that the notion of a single industry-specific ranking strikes the fleetness/flexibility advocates as an archaically misleading indicator; from a performance point of view, it's not your traditional competitor that matters but who else is in the "arena" with you, engaging and competing for the same customers but often with a different selling orientation.

It is equally wishful thinking to presume that the barriers to entry to biopharmaceuticals remain high enough to discourage would-be competitors attracted by the high margins and market exclusivity conferred by patents. If the industry's traded currency is now not the pill itself but the information that evidences outcomes, which in turn sets the condition for payment, then can it not be said that Google is also a drug company? How do we define our products in an era when a nerve signal generated by an artificial electrical impulse can produce the same physiological and therapeutic effect as a chemical drug?

Posing such basic questions illustrates how fundamentally the competitive set for big Pharma has changed. Finding the correct coordinates for this endless cycle of re-positioning is just as important as a winning scientific hand. Strategy experts like McGrath describe the necessary strategic response as "continuous morphing," and there is no Excel spreadsheet to furnish management with that traditional salve of certainty. All of this draws me to conclude that, assuming the series survives, our Pharma 50 of 2025 will test our current boundaries of comprehension. Yet, I am confident that this is still the one business I can say will help me live to see it.

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Pharmaceutical Executive

VOLUME 34, NUMBER 6

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On The Cover: Getty Images / Daryl Solomon

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PHARMACEUTICAL EXECUTIVE VOLUME 34, NUMBER 6 (Print ISSN 0279-6570, Digital ISSN: 2150-735X) is published monthly by Advanstar Communications Inc., 131 W. First St., Duluth, MN 55802-2065. Subscription rates: $70 (1 year), $125 (2 years) in the United States and Possessions; $90 (1 year), $145 (2 years) in Canada and Mexico; $135 (1 year), $249 (2 years) in all other countries. Price includes air-expedited service. Single copies (prepaid only): $7 in the United States, $9 in all other countries. Back issues, if available, are $20 for the United States and Possessions, $25 for all other countries. Include $6.50 per order plus $2 per additional copy for US postage and handling. If shipping outside the United States, include an additional $10 per order plus $3 per additional copy. Periodicals postage paid at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to *PHARMACEUTICAL EXECUTIVE*, PO Box 6180, Duluth, MN 55806-6180. Canadian G.S.T. Number: r-12421 3133rt001, Publications mail agreements NO. 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, Canada. Printed in the USA.

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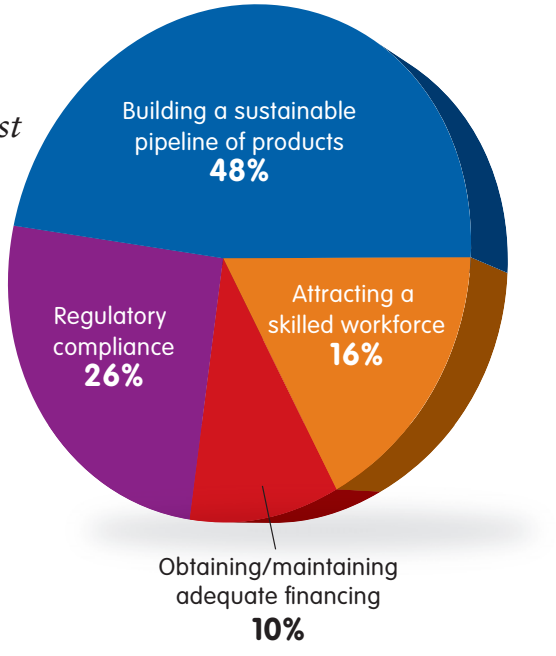
Most-read stories online: April 25 to May 24, 2014

Data Point

Poll data courtesy of online *Pharm Exec* readers between April 6 and April 30, 2014

Q: Which of the following business challenges poses the greatest threat to your company?



Readers Weigh In

All stakeholders are at fault in the current crisis of antibiotic resistance. Prizes are not going to create the new class of drugs that are needed. The life blood of innovation is cash flow during the new drug discovery and development process – not at the end like a diploma at graduation.

Ansis, 5/15/14
"Antibiotics Discovery: Time for a 'Manhattan Project'"
bit.ly/1tn77yo

Governments are supposed to govern in the nation's interest. I can't see how a takeover predicated solely on tax advantages for Pfizer is in the UK plc's interest. What is there to stop Pfizer moving its tax operations from the UK if it later decides another country is more attractive?

SteveB, 5/6/14
"Pfizer-AstraZeneca: Implications for the Future of Int. Pharma"
bit.ly/1nupZhq

Hepatitis C has few charities, little organization, and is misunderstood. Its victims are commonly looked upon as drug addicts. They don't speak with one voice so there's little risk to insurance providers who want to cheap out with people's lives.

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Dealmakers Roundtable

Pharm Exec sits down with experts from big Pharma, biotech, and the investment community to dissect the 2014 dealmaking landscape, and steps for success.

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What price innovation?

Payers, drug plans seek clear assessment of drug value to rationalize high drug prices.

Americans want new life-saving medicines that cure serious conditions and are affordable, as well as safe and effective. They still prefer market competition to accomplish this, recognizing that government-funded research, together with appropriate regulatory oversight, has created a public-private collaborative approach that has made the U.S. the predominant source of cutting-edge biopharmaceutical innovation in the world. Genetic discoveries and new technologies continue to spur new research, raising optimism that more new drugs will emerge, able to prevent and cure many serious health conditions afflicting millions of patients in all regions. Yet, changing markets and public funding pressures require new ways for U.S. health programs and private payers to evaluate the cost of increasingly expensive innovation.

These issues have moved to center stage due to mounting concern over the high price for Sovaldi (sofosbuvir), Gilead's new therapy for hepatitis C virus that generated a record-breaking $2.3 billion in revenues for its first quarter. Johnson & Johnson's Janssen Therapeutics' new hepatitis C treatment, Olysio, costs $66,000 for 12-week treatment, slightly less than the $88,000 for Sovaldi. But because millions of patients with hepatitis C may be candidates for treatment, total outlays will soar more. Payers fear, moreover, that coverage decisions for Solvaldi will set the stage for similar action on a wave of important new treatments for serious chronic conditions such as Alzheimer's disease and diabetes; a new class of drugs for certain high cholesterol patients may have an even bigger cost impact than the new hepatitis treatments.

Changing markets and public funding pressures require new ways for U.S. health programs and private payers to evaluate the cost of increasingly expensive innovation.

Oncologists face related issues, as the cost of branded cancer therapies has increased to $10,000 a month from $5,000 a decade ago, according to a report from the IMS Institute for Healthcare Informatics. The American Society of Clinical Oncology has published targets for "meaningful" clinical trial outcomes to encourage patients and physicians to look closely at treatment value. ASCO also has proposed a bundled payment system to simplify reimbursement and equalize financial incentives for prescribing oral versus injectible cancer drugs.

Pharmacy benefit managers (PBMs) and health plans are looking to manage rising drug expenditures by discouraging inappropriate prescribing, encouraging adherence by patients likely to benefit, and promoting approval of similar, competing drugs by the FDA to generate competition able to drive down prices.

Steve Miller, chief medical officer at Express Scripts, acknowledges that Sovaldi is "a much better drug" than previous hepatitis C therapies, which had serious side effects and required months of treatment. But the potential outlay for the drug is unprecedented, he pointed out at the recent Pharmaceutical Care Management Association (PCMA) policy forum. "Innovation doesn't have to cost more," he said, citing cost-cutting discoveries in other markets and countering the usual pharma claim that costly new medicines reduce downstream provider outlays.

Miller also complained that Sovaldi costs less in other countries, putting U.S. companies at a competitive disadvantage in the global marketplace. A $900 price tag in Egypt, Miller noted, creates a strong case for widespread "medical tourism."

The situation is even more dire for state Medicaid programs, which often have open formularies that cover most approved drugs. While new, effective cures for disease are exciting, noted Matt Salo, executive

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director of the National Association of Medicaid Directors, states are "in a panic" about how to pay for the 4-5 million patients in the U.S. with hepatitis C, many covered by Medicaid. Colorado and Pennsylvania have said they will limit Sovaldi to patients with advanced liver disease, and delay treatment for others. The Department of Veterans Affairs and the California Technology Assessment Forum take a similar position, despite charges of "rationing" from patient advocates.

Streamlining R&D

The prospect of even more high-cost specialty drugs has spurred initiatives to make drug development and clinical research more efficient. There's interest in more public-private collaboration on new research tools and faster identification of potentially effective compounds. Many of the recently negotiated billion-dollar corporate acquisitions and asset exchanges aim to strengthen drug development pipelines by shifting a company's focus to treatment areas where they have greater expertise. That strategy may be effective, as seen in warnings from payers that pharma research consolidation will reduce market competition.

FDA has adopted multiple strategies to speed drug development and review. The breakthrough drug designation is a "game changer" for addressing serious, life threatening conditions, commented Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), at the annual meeting of the Food and Drug Law Institute in April. CDER received 144 requests for breakthrough designation through April 4, granted 40 and denied 70, Woodcock reported, noting that the requests are not just for cancer drugs, but also for antivirals and other conditions. Last year, nearly half of all new molecular entities approved by FDA took advantage of some expedited review pathway, and several were approved in less than six months.

A related idea, designed to minimize the impact of new medical technologies on rising health care expenditures, is to extend FDA mechanisms for expediting approvals to drugs also likely to cut costs. A recent Rand Corp. study on "Redirecting Innovation in U.S. Health Care" further proposes more coordination between FDA approvals and Medicare coverage decisions, which again would favor money-saving technologies. FDA and Medicare consideration of cost issues in regulatory and coverage decisions would require legislation, as well as methods for determining how and when a new product truly has economic benefits.

These discussions may lead to adoption of specific Congressional proposals, possibly through legislation to renew prescription drug user fees for 2017. There are bills before Congress to expand incentives for developing new antibiotics to address drug-resistant infectious diseases, and growing concern on Capitol Hill about rampant abuse of prescription painkillers and opioids. These issues may gain impetus as negotiations between FDA and industry on PDUFA VI move forward in the coming year. PE

Congress weighs innovation

The need for new laws and regulatory policies to promote biomedical innovation is under examination by the House Energy & Commerce Committee's "21st Century Cures" initiative. Committee chairman Fred Upton (R-Mich) and leading Democrat Diana DeGette (D-Col.) emphasize the bipartisan nature of the undertaking and collaboration with FDA and the National Institutes of Health (NIH) in seeking ways to streamline new medical product development. An initial white paper questions whether randomized, blinded clinical trials that compare the effect of a drug over time on large numbers of patients is always the best approach, as "timelines, size, failure rates and costs of conducting trials are at all-time highs." The policymakers note that FDA may need to change its structure and management to more rapidly incorporate innovative approaches and technologies into its review process, in addition to supporting numerous partnerships to develop new biomarkers and modernize clinical trial operations.

The committee launched its investigation last month with a roundtable discussion on the state of U.S. biomedical innovation, raising the specter that China and other nations will gain preeminence in the field without major policy changes. NIH director Francis Collins stressed the need for greater and more predictable funding for NIH research, and Janet Woodcock cited strategies for improving the clinical trial process.

Front & Center

Sensei Labs, New From Klick Health, Helps Biotechs Evolve and Execute Faster

Marketing approval from the Food and Drug Administration is a major milestone for any early stage biotech, yet it also presents a host full of new challenges.

The skills needed to commercialize a new product are not the same skills needed to develop a drug candidate and shepherd it through the clinical trial process. The internal workflows and communication channels that functioned so smoothly during the research-and-development phase can quickly become strictures that threaten to choke the quick commercial expansion needed to meet market expectations. What is the savvy CEO to do?

For most, the trend has been to bring in entirely new leadership to grow the business. But that's only half the battle, especially when it comes to helping manage the change internally. Enter Sensei Labs.

Sensei Labs is the newest innovation from Klick Health, the largest independent digital health agency in the world. Over the years, CEO Leerom Segal and his team have become experts in using data internally to drive their business, in much the same way Amazon, Facebook, Netflix and other technology leaders use customer analytics as profiled in the New York Times bestselling book, "The Decoded Company: Know Your Talent Better Than You Know Your Customers" (Portfolio/Penguin) that Segal co-wrote.

Sensei Labs uses the same data-centric approach to transform R&D-stage, and rapidly scaling biotech companies into optimized commercial entities. To find out how Sensei Labs helps biotechs make the transition efficiently and with confidence, *Pharmaceutical Executive* spoke with Segal and fellow co-author Jay Goldman, Klick's Managing Director.

Klick Health's Leerom Segal and Jay Goldman help biotechs optimize and reach their full potential with their latest innovation, Sensei Labs.

What exactly does Sensei Labs do?

Segal: We help biotechs evolve and execute faster. For example, we help emerging biotech companies go through the massive transformation that happens when they go from being small and largely R&D based to larger commercial entities. And we also help established biotechs ramp up for new product launches and any other developments involving rapid scaling. There's a tremendous opportunity for these companies to leverage the abundance of new technologies and capabilities that have made consumers' lives easier. We start the process by asking a deceptively simple question: What happens when your organization understands your people as well as you understand your prescribers? The answer opens the door to a significant advantage that gives biotech executives more time to focus on their core competencies.

Goldman: The idea for Sensei Labs really began when Klick's clients asked us for advice on how to scale their operations upon receiving product approvals or after M&A activity. We have a proven history identifying and codifying repeatable successes and we recognized that these clients were encountering a very predictable set of challenges that we have solved in the past. The challenges of commercialization may be new to a particular organization, but they are not new to the industry. We have specialized, experienced teams who have made this transition multiple times to help companies manage and control the change process.

What are the typical challenges that companies face with that initial product approval?

Goldman: Very often, you have a biotech that has been in the R&D space for a decade or more and finally gets a letter from the FDA that gives them confidence that a particular candidate is going to be marketed. Usually, the leadership has a clinical background so they very rapidly try to staff up the commercial organization to oversee the marketing, sale and all the support functions that enable the commercialization process.

This translates to an incredible amount of change in a very short time frame. You can imagine that a company, which has been in business for a decade, has a very specific culture. But if more than half the headcount is new, that company can run into significant problems unless it is very deliberate about spreading the belief system and sustaining the culture that has made it successful, the ways it wants to operate, and the tools it uses to operationalize those beliefs and goals. Sensei Labs helps turn that vision into an actionable plan.

Part of what we do involves consulting services on how to get from the current state to a desired end state. But most of what we provide is in the form of building the actual technology and tools that help make the transition possible and orchestrate all of those functions as efficiently as possible.

Can you give us an example?

Segal: Acorda Therapeutics is a company with whom we had been working. The company had already been commercialized, but its CEO, Ron Cohen, was very prescient. He had been through the process before and he understood the necessity of having a deliberate approach to culture that ran through the company, everything from internal communication to rep enablement. We helped their team operationalize and execute an array of initiatives they understood and knew they needed. For example, discipline around how to manage digital programs along with support actualizing the execution of the workstreams themselves.

What key tools do companies need to commercialize?

Segal: We begin by building the communication tools that most emerging biotechs have never needed before. When you've got a small team, it's easy to get situational awareness by just looking over your shoulder.

So very often we need to take all of their offline artifacts and tools and help them digitize them. We also will get involved in building internal portals or communication platforms, as well as basic tools to help them navigate their workflows. Consider how a company that hasn't been commercialized has never previously needed to get a document from Medical, to Regulatory, to Legal, and all those steps along the way.

They're doing these workflows for the first time so the more we can accelerate the process, using tools that are built on practices that are proven, the easier we can make it for them to get to market in a way that's predictable and consistent.

How does this differ for more mature companies or acquisitions?

Goldman: Different growth curves present different challenges. Many very mature companies have enjoyed a rocket-like growth engine that becomes harder and harder to fuel as they get larger. Acquisitions present their own set of challenges as the buyer tries to integrate a large set of new employees, a different culture, and a whole network of systems and processes with minimal disruption. Both present a number of opportunities to optimize through the creative application of technology and data.

What history do you have in this area?

Segal: Sensei Labs is staffed with digital natives, the same digitally savvy people who helped us launch Klick 17 years ago. Digital is our way of life, something we are so intimately familiar with that when we talk with clients, there is no aspect of digital within their organizations that we can't help them with.

How is the market responding to your ideas?

Goldman: The market as a whole is responding very positively. "The Decoded Company," the book in which the philosphy behind Sensei Labs is laid out is a *New York Times* bestseller and is garnering a ton of press with top media like *Fast Company, Wired, Bloomberg,* and *Business Insider.* More importantly, we have been finding that current and prospective clients are keen to adopt the principles outlined in the book. We're working with a number of biotechs at various stages in their Decoded journey.

What's ahead for the future?

Segal: We have a lot to offer early-stage and rapidly scaling biotechs in terms of helping them optimize and realize the full potential of what they have in their pipelines. Sensei Labs would like to help them transform into vibrant companies that expand and grow.

Goldman: Absolutely, and the timing couldn't be better. The industry is finally catching up to digital. If you look at the FDA's recent draft guidance around social media and third-party content, it is no longer asking for screen shots. It is asking for URLs directly, which is a big step forward. The guidance around third-party content is very positive and on the right track.

Compassionate Use Requests Complicate Drug Development

Pharma, HCPs, and regulators walk tightrope in addressing early-access push while supporting biomedical R&D.

A national publicity campaign recently succeeded in obtaining early access to an experimental treatment for a seriously ill child, touching off a broader discussion of compassionate use policies and their impact on drug development and approval. As 7-year-old cancer patient Josh Hardy gained relief from a life-threatening infection following a bone marrow transplant, thanks to Chimerix's promising new antiviral drug brincidofovir, hundreds of patients turned to the Internet and social media to intensify pressure for similar compassionate access. The trend demonstrates the need for sponsors, health professionals and government regulators to find new ways to handle these difficult requests, while also supporting clinical research and biomedical R&D.

Biopharmaceutical companies receive dozens of requests for early access to promising therapies, but often turn them down. Clinical supplies usually are very limited, often just enough to conduct a study. Production costs for biologics are high, particularly for small firms struggling to finance complex research programs.

Moreover, sponsors fear that adverse events with patient populations outside a clinical trial could delay development and approval. And expanded access can interfere with clinical trial accrual; if patients can obtain treatment outside a regulated study, they won't want to enroll in a trial where they risk getting a placebo or a less effective comparator drug.

Diversion of resources to deal with individual access requests can delay development and stymie efforts to achieve equitable distribution of limited supplies.

The social media phenomena raises serious ethical issues about whether hard decisions about who gets access to scarce therapies should be made on the basis of catchy publicity campaigns and political pressure—as opposed to who is most seriously ill and who is most likely to respond to treatment. Some consider lotteries or independent third parties as fairer ways to decide how to distribute a scarce, highly valuable resource. The prime ethical obligation of biotech companies, says the Biotechnology Industry Organization (BIO), is to develop safe and effective drugs as quickly as possible so that broad patient populations can benefit. Diversion of resources to deal with individual access requests can delay development and stymie efforts to achieve equitable distribution of limited supplies.

Regulatory challenges

FDA's process for facilitating expanded access requests is a prime focus of reformers. The agency permits clinical trial sponsors to amend an investigational new drug application (IND) to grant patients access to experimental drugs for treatment purposes. Patients can't apply for such access; the request has to come from the sponsor, physician investigator, or a qualified treating physician, either for a single patient or a small group (up to 100 patients). The expanded access IND requires evidence that the individual(s) have serious or life-threatening conditions, do not qualify to participate in a clinical trial, have no other treatment options available, and that potential benefits are likely to outweigh possible risks.

Details on the process are provided on FDA's website and in a May 2013 Q&A guidance on expanded access to investigational drugs for treatment use. Jim Robinson, president of Astellas US, would like to see additional guidance on criteria for vetting requests for compassionate use, noting that demands for early access will only increase with some 3,000 drugs in development for cancer and other serious conditions.

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The social media phenomena raises serious ethical issues about whether hard decisions about who gets access to scarce therapies should be made on the basis of catchy publicity campaigns and political pressure—as opposed to who is most seriously ill.

FDA's Office of Health and Constituent Affairs, which provides information to health professionals and patients on expanded access policies and procedures, reports that the agency receives about 1,000 expanded access INDs and access protocols each year and approves virtually all of them. The vetting process includes review by an institutional review board (IRB) to ensure adequate informed consent, and by the relevant new drug review division.

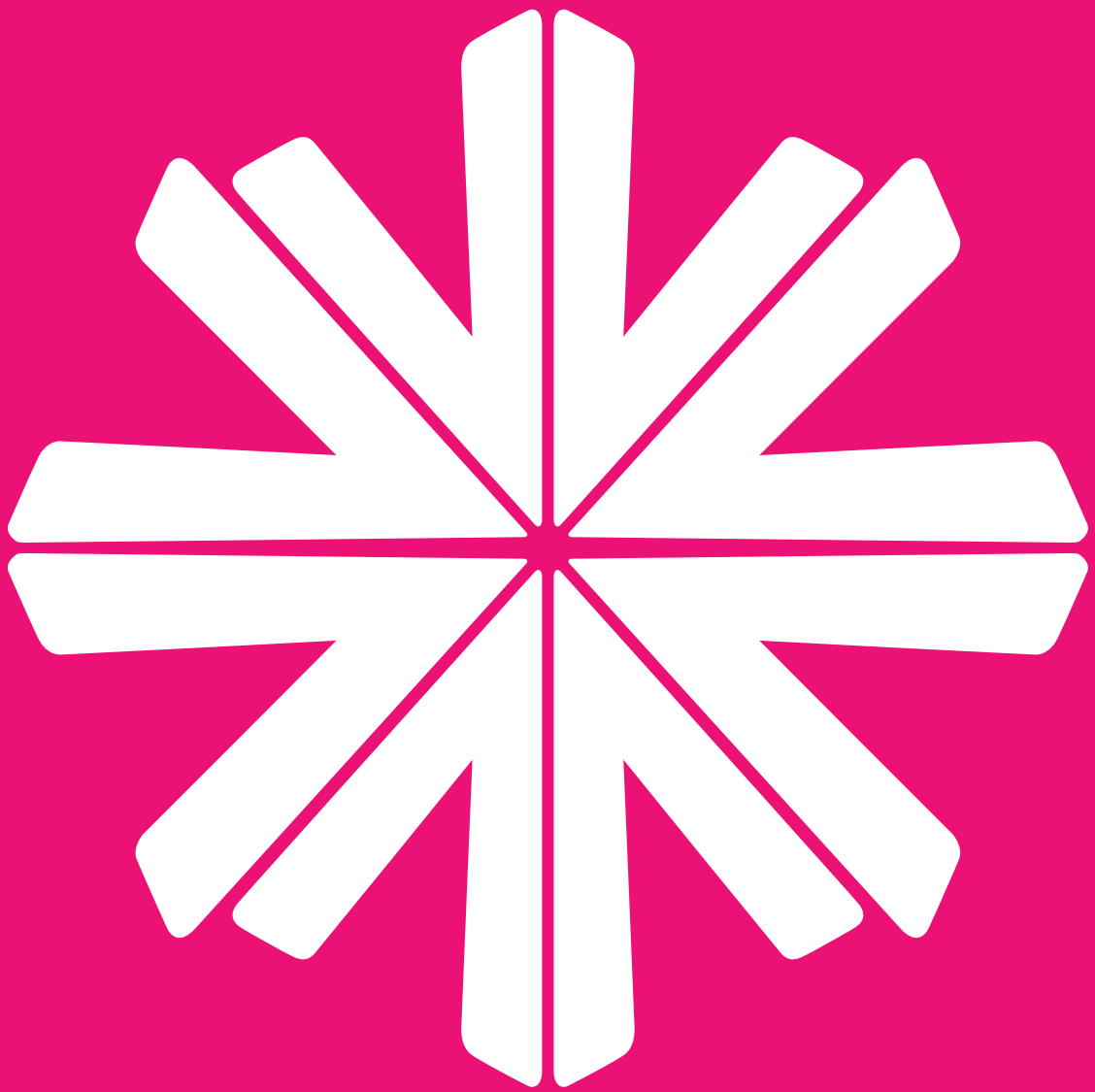
FDA officials sometimes convey patient requests to pharmaceutical companies and offer assistance to willing firms and physicians in filing necessary information and navigating the application process, explains Patient Liaison Program director Richard Klein. Because the purpose of these programs is treatment, and not research, sponsors don't have to submit efficacy data from an expanded access study, but must report serious adverse events.

While FDA permits sponsors to charge patients for the cost of drugs provided under compassionate use, this provision is seldom used. Companies usually prefer to keep confidential information on production processes and costs, and limited supply is a larger concern than gaining revenue.

FDA's desire for flexibility can be seen in its handling of the Chimerix case. Amidst the public demand for access to brincidofovir for Josh Hardy, FDA worked with Chimerix to approve a 20-patient open-label clinical trial for treatment of adenovirus infection in immunocompromised pediatric patients. The company thus avoided a massive open-access program, and gained a strategy that it hopes will lead to a Phase III trial for this indication. Meanwhile, Chimerix is continuing its main development program (under new company leadership), which seeks accelerated approval of the drug for prevention of the more common cytomegalovirus (CMV) infection in adult bone marrow transplant patients. Chimerix launched its Phase III SUPPRESS trial last year at 40 transplant centers, with an eye to enrolling 450 patients, 150 receiving placebo; initial results are expected by mid-2015.

Although FDA and the sponsor addressed this compassionate use case successfully, there's continued pressure for new approaches. A bill before Congress would permit the manufacture, importation, and distribution of unapproved investigational products to terminally ill patients. State legislatures are considering "right to try" bills, as seen in an Arizona measure that permits physicians to prescribe investigational drugs for certain terminally ill patients. Such proposals raise constitutional questions about the right of states to challenge federal drug approval policies, an issue central to past lawsuits challenging FDA interference in patient treatment.

Faster approval of important new medicines could address some early-access concerns, a goal for regulators and sponsors alike. FDA held a public hearing in February 2013 on strategies for improving the accelerated approval process and whether FDA needs additional tools and authority to move promising therapies through the regulatory process—issues that will be explored further. PE



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Hopes High as EU Heads Into Leadership Change

Rare allies—Innovator and generic pharmas—are calling for policy integration in Europe. But ideology and newfound scepticism on the merits of drugs in healthcare could complicate the effort.

For European business, the perils of the immediate past are being replaced by the promise of the future, as the financial crisis appears to recede, and the prospect beckons of new opportunities under a new European Parliament and a new European Commission (EC). Last month's European Parliament elections will bring many fresh faces to Brussels, and every lobby group in town is already planning how to win their attention and hopefully their favor. Of even more significance, a new Commission is due to take office in November, replacing the timid and tired ten-year administration of José Manuel Barroso with—it is hoped—a team bursting with renewed dynamism and energy, and with a readiness to listen to well-formed policy pitches.

Push for integration

It is against this background that the principal drug industry associations in Europe launched a call in mid-May for "an integrated European industrial policy for the pharmaceuticals sector." The industry has achieved its own integration in putting this plea together. It unites—in a rare show of solidarity—both the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Generic Medicines Association (EGA). The conflicting interests of the research-based and generic companies have often kept them apart, but they have started to work together much more closely in Europe, partly because of the tougher conditions they all face, and partly because shifts in ownership and in corporate strategy have blurred many of the distinctions that were so clear in the past.

So, now they are, as they say themselves, "joining forces." The industry groups launched their appeal at the annual EU Business Summit, taking advantage of its theme this year, "The Business Agenda 2014-2019: Rebuilding a Competitive Agenda." The drug industry associations' particular angle is that Europe's healthcare systems have suffered from economic recession and austerity policies, and this has affected access to healthcare for EU citizens. Their response is to urge promotion of "an integrated life sciences industry for Europe" that will serve the health of society and economic prosperity.

The campaign that EFPIA and EGA are conducting focuses on three priorities. First, the groups want a clear recognition that medicines are essential to improve patient outcomes and equity of access to healthcare across Europe. Then they want a more predictable business environment so as to give the industry incentives to invest and to bring "better and more cost-effective treatments" to patients. And alongside, they want a context that will "make the EU an attractive global hub for pharmaceutical research and manufacturing."

Not so simple

These may all seem, at first glance, to be reasonable, even laudable, objectives, unlikely to run into opposition from anyone. But there is more to the campaign than meets the eye. That first priority of recognizing the importance of medicines in European healthcare is not quite so obvious as it looks. There has been a rising tide of concern in Europe about the role of medicines over recent years.

Part of this has sprung from politics—perhaps, more aptly, from ideology. Distrust of industry in general, and of the healthcare industry in particular, is more evident in Eu-

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

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ropean public discourse every day. A long tradition of what started as rather lonely dissent—going back to the days of Andrew Herxheimer and Charles Medawar in the 1980s—has matured into organized opposition, now manifested in the popular acclaim and high public profile that greets the Ben Goldsteins of latter-day Europe. This has been compounded by a loose but increasingly influential anti-science movement that ranges from the advocates of homeopathy to the more muscular international civil society organizations capable of mobilizing thousands of supporters onto the streets with a finely-phrased leaflet on genetically modified crops.

Influences beyond ideology

As long as the negativism was inspired by ideology, it was possible to contain and to counter. But the new ingredient in the mix is the scepticism discernible among economists about the merits of medicines in healthcare. Until recently, only zealots liked to draw attention to the huge disparity between spending on prevention and spending on medicines Now it features routinely in official documents from national treasury ministries and the EU Council of ministers of finance and economic affairs. And it is never absent from any of the numerous governmental and intergovernmental reflections on that new holy grail of sustainable healthcare systems.

In other words, the old certainties are no longer valid. While elimination of medicines entirely from healthcare remains a view espoused only by the most radical, severe curtailment of the spending on medicines in general is now common currency. The industry that makes them is having to fight as never before against views that were, until now, the preserve only of eccentrics.

The "predictable business environment with incentives to invest" is just as challenging an objective. It is hardly necessary to point to the current unpredictability of the world economy and the still-fragile European recovery, and its obvious implications for the feasibility of a predictable business environment. Much of that, however, is in the lap of gods far more potent than those that stoop to the concerns merely of the pharmaceutical industry. But the aspiration for incentives to invest does fall fully into the regulatory and economic arena, where health ministers, industry ministers, and economic affairs ministers hold sway. And this is no easy terrain. The term "incentives to invest" is just the latest variation on the theme that goes back decades—to the era of the Bangemann roundtables and before—when attempts were first being made at European level to square that intractable circle of prices sufficient to fuel the research cycle.

The old certainties are no longer valid. While elimination of medicines entirely from healthcare remains a view espoused only by the most radical, severe curtailment of spending on medicines in general is now common currency.

Indeed, as the costs of drug development have soared, the terrain has become yet more difficult. New treatments for hepatitis C virus, cancer, or multi-drug resistant tuberculosis are emerging, but at prices that discourage healthcare paying agencies from accepting their use. In turn, this discourages the shareholders of pharmaceutical companies from entertaining the research programs that can deliver innovative treatments. And despite all the heady recent talk of risk-sharing and public-private partnerships, there is still little sign of workable new business models that can offer the incentives being sought.

As to making the EU "an attractive global hub for pharmaceutical research and manufacturing," the scale of the challenge can be easily demonstrated by the recent avid interest of Pfizer in AstraZeneca (because the EU is still an attractive global hub, etc.) and the alacrity with which pharmaceutical companies are disengaging from Europe's more troubled markets—and switching to Asia and Latin America. Conserving some of the EU's member states as attractive hubs may be possible—although more through national than European action—but trying to make the EU as a whole an attractive hub is a venture certain to disappoint, and probably doomed to failure.

Well might the generic medicines industry boast—as it does in this joint pitch—that it is investing in new manufacturing sites and increasing growth and jobs across Europe. And well might EFPIA speak—as it does—of employing 700,000 people.

Expand the dialogue

The claims are doubtless true. But if they demonstrate anything, it is the industry's current prosperity. Not a recipe and not a justification for meeting the challenges the industry says are so vital to its interests. "With the EU elections approaching, there is no time like the present to start talking with potential leaders of tomorrow about how to pave the path towards a healthy EU in the future," concludes the industry announcement of its campaign. Start talking, yes. But come up with some decent arguments if you want to win the debate. PE

The Long Tail

Therapeutic specialization, competitive differentiation, and a finely-tailored value proposition are creating a new drug world of bespoke market niches—and infinite future possibilities for the best of this year's Pharma 50.

The vigorous return of M&A activity to biopharmaceuticals this year brings us back to the question that industry strategists have been posing for years: is more size and scalable efficiencies the best solution to the declining market power of pharmaceuticals in an endlessly restructuring healthcare system? Anecdotal evidence combined with some discomfiting statistics on pipeline productivity among the biggest M&A combinations of the past 15 years suggests that the answer is no—and the latest annual iteration of our Pharma 50 rankings bears this out.

That's because Pfizer, the one company most associated with the "mega merger" strategy, has ceded its position at the very top of our list for the first time since 2002. It traded places with last year's number two, Novartis, whose management recently made the switch from broad diversification to a "grow to get small" strategy that eschews the blockbuster model for the development of numerous drugs for smaller target populations—and where specialization around science and unmet medical need is more determinative than market size and reach. Equally indicative is the steady ascent of Roche, to third place from fifth last year, as its single-minded focus on oncology and the diagnostics that deliver evidence to prove value continues to make inroads with payers and patients alike.

Bolstering the thesis even further is the continued strong performance of those companies with an unambiguous commitment to the hot specialty segment. Gilead, for example, moves up in our ranks to 18th in sales from 23rd in 2010, while Biogen Idec jumped from the 36th spot to 27th over the same period. Likewise, Celgene has soared to 26th from its lowly 41st place just four years ago.

In fact, one of the clearest indicators of success on the sales front is leadership in biologics and specialty drugs, where the ability to address an underserved patient segment with permeable price points is producing a bumper crop of "mini-blockbusters" with long-staying power and the scientific bona fides needed to seed multiple additional indications. It's one reason why we decided, as a backdrop to this year's list, to ask our colleagues at the IMS Institute for Health Informatics to take the microscope to this segment to analyze just how much longer these good times have to run, particularly as the market for specialty goes global.

One final observation: applying the size and scale measure to R&D offers little comfort concerning the crucial financial relationship between an enterprise's draught weight and returns on every dollar invested in new drug development. The top 10 revenue producers on this year's list spent more than $60 billion on R&D, yet most of the more interesting new therapies continue to spring from the middle-range of companies, below the top rank. And the resource gap is stark. Our one new entrant to the Pharma 50 this year, South Africa's Aspen Pharmacare, managed to rack up just south of $3 billion in global sales, mostly in hotly contested emerging country markets, while spending a trifling $1.6 million on new drug R&D—approximately the same as what our top-of-the-league player, Novartis, spends every 90 minutes, every day of the year. All you sizeocrats and scaleanistas take note: Could it really be how you spend that counts?

— William Looney, Editor-in-Chief

Photo: Thinkstock

Pharma 50 Insight:

The Accelerating Growth of Specialty Markets

By Waseem Noor and Michael Kleinrock, IMS

A highlight of the Pharma 50 ranking over the last few years is the steady upward trajectory of companies with a strong franchise in specialty medicines. Specialty markets are appealing to companies that have a strong research and development pipeline, are prioritizing serious unmet medical needs, and are taking a more personalized approach to the traditional relationship between physicians and patients. This is why we find it appropriate to examine in more detail the factors that drive success in the specialty drug market as well as likely key areas of growth in this segment over the next five years.

Overall, this market has experienced significant expansion since the turn of the decade, with steady gains

Rank	Company headquarters [website]	2013 Rx Sales (USD in mln)	2013 R&D spend (USD in mln)	2013 Top-selling Drugs [USD in mln]
1	**Novartis** **Basel, Switzerland** [novartis.com]	**$46,017**	**$9,360.3**	**Gleevec** [4,693] **Diovan** [3,524] **Lucentis** [2,383]
2	**Pfizer** **New York, New York** [pfizer.com]	**$45,011**	**$6,254.0**	**Lyrica** [4,595] **Prevnar 13** [3,974] **Enbrel** [3,774]
3	**Roche** **Basel, Switzerland** [roche.com]	**$39,143**	**$8,293.5**	**Rituxan** [7,503] **Avastin** [6,751] **Herceptin** [6,562]
4	**Sanofi** **Paris, France** [sanofi.com]	**$37,701**	**$6,117.4**	**Lantus** [7,592] **Plavix** [2,460] **Lovenox** [2,262]
5	**Merck & Co** **Whitehouse Station, New Jersey** [merck.com]	**$37,519**	**$7,123.0**	**Januvia** [4,004] **Zetia** [2,658] **Remicade** [2,271]
6	**GlaxoSmithKline** **Brentford, England** [gsk.com]	**$33,055**	**$5,041.0**	**Seretide/Advair** [8,251] **Pediarix** [1,349] **Avodart** [1,341]
7	**Johnson & Johnson** **New Brunswick, New Jersey** [jnj.com]	**$26,475**	**$5,810.0**	**Remicade** [5,334] **Zytiga** [1,698] **Prezista** [1,673]
8	**AstraZeneca** **London, England** [astrazeneca.com]	**$24,523**	**$4,269.0**	**Crestor** [5,622] **Nexium** [3,872] **Symbicort** [3,483]
9	**Eli Lilly** **Indianapolis, Indiana** [lilly.com]	**$20,119**	**$5,316.2**	**Cymbalta** [5,084] **Alimta** [2,703] **Humalog** [2,611]
10	**AbbVie** **North Chicago, Illinois** [abbvie.com]	**$18,790**	**$2,831.0**	**Humira** [10,659] **AndroGel** [1,035] **Kaletra** [962]

Sources: Company financial statements, SEC 10k reports, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys.

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experienced across all geographies. Specialty pharmaceuticals comprised 19% of total global sales in 2008; in 2013, it reached 24%. More important, growth in the segment outpaced overall sales. Whereas, global sales of all pharmaceutical products in absolute terms rose from around $700 billion in 2008 to $880 billion in 2013—a 25% increase, according to IMS Health's MIDAS database—the specialty drug portion expanded at double the rate, at about 50% in absolute terms.

The conventional wisdom is to define specialty as products that treat smaller patient populations with higher treatment costs. In order to provide a consistent classification, IMS Health defines specialty products as medicines that treat specific, complex diseases with five or more of the following attributes:

- Use in treatment of chronic conditions.
- Initiated by a specialist.
- Requiring special handling and administration, including subcutaneous injection.
- Subject to unique distribution arrangements.
- High price points.
- Extensive patient care service, monitoring, or education.

In countries where individual patients bear a significant portion of the out-of-pocket costs of treatment, companies must deploy and fund novel approaches to increase disease awareness and identify patients at risk.

The trend in favor of specialty shows every sign of continuing. Specialty products now represent a larger portion of the biopharma R&D pipeline: we estimate that more than 50% of early- to late-stage pipeline compounds are specialty products. In addition, these products are selling outside the traditional geographic markets of the US, EU5, and Japan. There is an assumption that high prices limit the potential for these drugs in these non-traditional markets—in fact, sales are growing, though not always for the originators of the molecules.

As companies continue to invest in this space, a key area of interest is better understanding of the historical growth trends in specialty. Such context is critical to answering this question: which are the areas that Pharma 50 companies should concentrate their investments to expand and grow into the next decade?

Rank	Company headquarters [website]	2013 Rx Sales (USD in mln)	2013 R&D spend (USD in mln)	2013 Top-selling Drug [USD in mln]
11	**Amgen** Thousand Oaks, California [amgen.com]	$18,192	$3,941.0	Enbrel [4,551]
12	**Teva Pharmaceutical Industries** Petach Tikva, Israel [tevapharm.com]	$17,563	$1,422.0	Copaxone [4,328]
13	**Bayer** Leverkusen, Germany [bayer.com]	$15,594	$2,710.0	Kogenate [1,597]
14	**Novo Nordisk** Bagsvaerd, Denmark [novonordisk.com]	$14,886	$2,089.9	NovoRapid [3,001]
15	**Boehringer Ingelheim** Ingelheim, Germany [boehringer-ingelheim.com]	$14,468	$3,246.7	Spiriva [4,719]
16	**Takeda** Osaka, Japan [takeda.com]	$13,591	$3,351.6	Biopress [1,256]
17	**Bristol-Myers Squibb** New York, New York [bms.com]	$12,306	$3,715.0	Reyataz [1,551]
18	**Gilead Sciences** Foster City, California [gilead.com]	$10,804	$2,056.4	Atripla [3,648]
19	**Astellas Pharma** Tokyo, Japan [astellas.com]	$10,431	$2,132.3	Prograf [1,755]
20	**Daiichi Sankyo** Tokyo, Japan [daiichisankyo.com]	$10,268	$1,925.9	Benicar [2,116]

Sources: Company financial statements, SEC 10k reports, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys.

Our analysis finds three answers to the question. First, building a truly global business requires developing assets in the specialty segment, if only because sales and volumes of these drugs are increasing in almost every geography. Market demand is turning more towards specialty products, and for the top integrated players represented in the Pharma 50, being able to meet this demand is an acute strategic imperative. Second, the market channel structure within the specialty field is changing, as more products are being sold in the retail sector rather than in hospital or specialty clinics. This opens significant new possibilities in terms of a broader audience reach, with a strong "willingness to pay" component. Finally, we are seeing therapeutic class concentration, with a potential impact on the future competition: the top seven therapeutic areas in specialty now seem to account for about 75% of all sales of specialty products.

In the EU5, there seems to be a higher proportion of specialty product usage than in the US, and a rise in both hospital and retail sales. This is being driven by adoption of newer therapies under the single-payer structure of these markets.

An important caveat in interpreting all figures in this article is that IMS sales data is based on the ex-manufacturer invoice price, exclusive of rebates, discounts, and patient access schemes. In some geographies (e.g., oncology in Europe), this could mean that the entire increase in sales does not translate directly back to the manufacturer because discounts to the price may be in place. Nevertheless, we are confident that the trends identified are representative of what is actually occurring in the market.

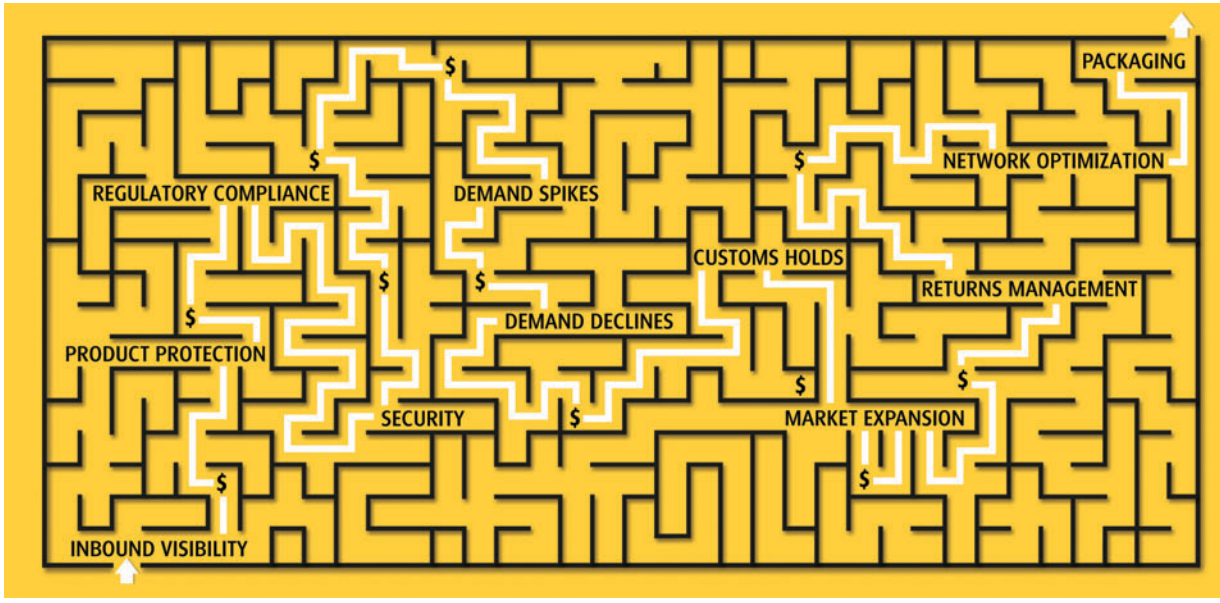
Geographic growth

As companies expand outside the mature US, EU5, and Japan triad, they

Rank	Company headquarters [website]	2013 Rx Sales (USD in mln)	2013 R&D spend (USD in mln)	2013 Top-selling Drug [USD in mln]
21	**Otsuka Holdings** **Tokyo, Japan** [otsuka.com]	$8,655	$2,032.6	**Abilify** [5,510]
22	**Baxter International** **Deerfield, Illinois** [baxter.com]	$8,265	$1,070.0	**Gammagard Liquid** [2,118]
23	**Merck KGaA** **Darmstadt, Germany** [merckgroup.com]	$7,913	$1,594.0	**Rebif** [2,477]
24	**Actavis** **Zug, Switzerland** [actavis.com]	$7,206	$581.1	**Methylphenidate ER** [610]
25	**Mylan** **Canonsburg, Pennsylvania** [mylan.com]	$6,772	$456.2	**EpiPen** [829]
26	**Celgene** **Summit, New Jersey** [celgene.com]	$6,359	$1,650.4	**Revlimid** [4,280]
27	**Biogen Idec** **Weston, Massachusetts** [biogenidec.com]	$5,429	$1,444.1	**Avonex** [3,005]
28	**Allergan** **Irvine, California** [allergan.com]	$5,398	$1,034.7	**Botox** [1,982]
29	**Les Laboratoires Servier** **Neuilly-sur-Seine, France** [servier.com]	$5,058	$1,264.4	**Coversyl** [912]
30	**Abbott Laboratories** **Abbott Park, Illinois** [abbott.com]	$4,974	$239.0	**Biaxin** [416]

Sources: Company financial statements, SEC 10k reports, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys.

How the listings were compiled: *Pharm Exec* would like to thank EvaluatePharma for assisting in the development of this year's Pharma 50 listing. In the case of privately held companies and in some other instances, the numbers reflect a best estimate, based on a consensus methodology that includes forecasts from brokers covering these companies. All figures represent the fiscal year that ended in 2013. For most American and European companies, that means the year ending December 31, 2013. For many Japanese companies, we used the fiscal year ending March 31, 2013. Historic averages were used in the conversion of companies'native currency to USD.



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28 Pharma 50

have adapted their traditional commercial models to the customized needs of alternate geographies. For specialty products, this has posed a difficult challenge as treatments may require complex handling or levels of patient care that are hard to secure in areas with poor infrastructure and sporadic practice patterns. In addition, in countries where individual patients bear a significant portion of the out-of-pocket costs of treatment, companies must deploy and fund novel approaches to increase disease awareness and identify patients at risk. It is a necessary pre-condition to gain patient acceptance and position the local market for sales of higher priced therapies. It suggests higher fixed costs to developing the business there.

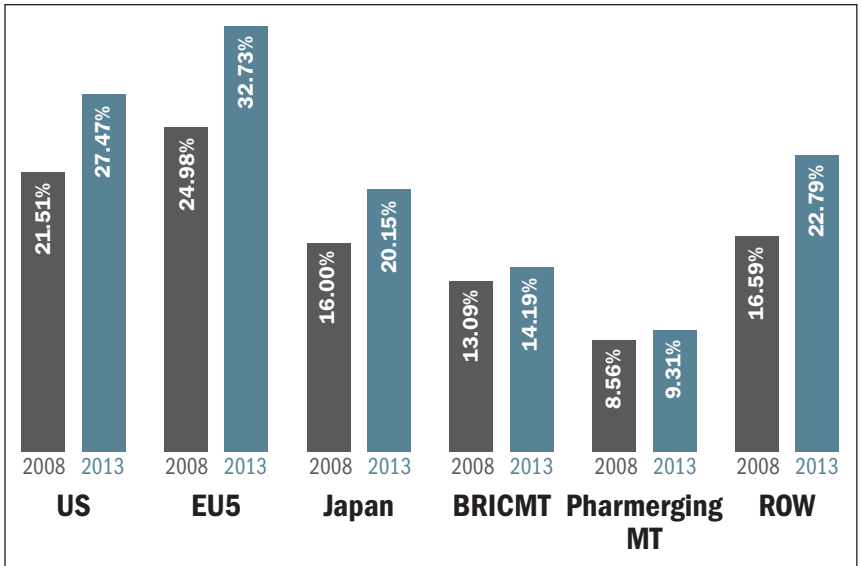

Figure 1: Specialty market percent of total sales by geography (Data: IMS)

Despite these challenges, the past few years have seen a significant increase in specialty sales and volumes across all geographies (see Figure 1). Using our proprietary information, we find that even with absolute growth in all the markets, the proportion of the specialty segment still increased. The increase was most prominent in the US, EU5, and Japan, with the proportion rising by at least five percentage points in each region. For example in the US, 27.5% of sales were in spe-

Rank	Company headquarters [website]	2013 Rx Sales (USD in mln)	2013 R&D spend (USD in mln)	2013 Top-selling Drug [USD in mln]
31	**CSL** **Melbourne, Australia** [csl.com.au]	$4,875	$427.1	**Privigen** [2,089]
32	**Shire** **Dublin, Ireland** [shire.com]	$4,847	$890.2	**Vyvanse** [1,228]
33	**Eisai** **Tokyo, Japan** [eisai.com]	$4,821	$1,318.0	**Aricept** [797]
34	**Valeant Pharmaceuticals International** **Mississauga, Ontario** [valeant.com]	$4,196	$156.8	**Solodyn** [214]
35	**UCB** **Brussels, Belgium** [ucb.com]	$3,802	$1,137.1	**Keppra** [946]
36	**Chugai Pharmaceutical** **Tokyo, Japan** [chugai-pharm.co.jp]	$3,648	$765.4	**Neutrogin/Granocyte** [234]
37	**Fresenius** **Bad Homburg, Germany** [fresenius-kabi.com]	$3,604	$336.1	**Heparin Sodium** [73]
38	**Mitsubishi Tanabe Pharma** **Osaka, Japan** [mt-pharma.co.jp]	$3,505	$703.8	**H1N1 HA flu vaccine** [152]
39	**Forest Laboratories** **New York, New York** [frx.com]	$3,380	$771.7	**Namenda** [1,537]
40	**Menarini** **Florence, Italy** [menarini.com]	$3,324	N/A	**Lobivon/Nebilet/Nebilox [301]**

Sources: Company financial statements, SEC 10k reports, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys.

cialty products in 2013 while the remaining 72.5% were primary care, OTC, and all other prescription products. This proportion increased from 21.5% in 2008, and was driven by new launches and broader adoption of existing treatments.

The geographies on the X-axis represent the market tiering approach employed by IMS Health. For example, what we call the "Pharmerging" markets are split into three tiers. Tier 1 is China, Tier 2 is India, Russia, and Brazil, and Tier 3 includes the remaining 17 Pharmerging countries that have greater than $25,000 per capita income, expressed on a purchase price parity basis, and have five-year pharmaceutical market aggregate growth of greater than $1 billion. Tier 3 countries include Algeria, Argentina, Colombia, Egypt, Indonesia, Mexico, Nigeria, Pakistan, Poland, Romania, Russian Federation, Saudi Arabia, South Africa, Thailand, Turkey, Venezuela, and Vietnam.

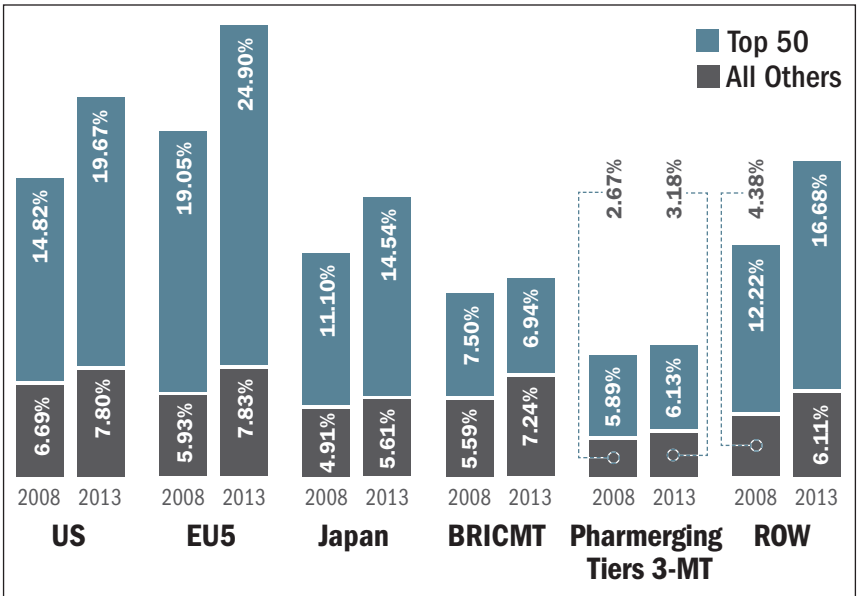

Figure 2: Specialty market percent of total sales by geography and by Pharma 50 (Data: IMS)

For this article, we diverged from the tier model and put Mexico and Turkey with the remaining BRIC countries to reflect the priorities of most pharmaceutical companies, and because these countries are more advanced in their adoption of specialty medicines. In addition, we have included non-retail sales for Brazil

Rank	Company headquarters [website]	2013 Rx Sales (USD in mln)	2013 R&D spend (USD in mln)	2013 Top-selling Drug [USD in mln]
41	**Dainippon Sumitomo Pharma** **Osaka, Japan** [ds-pharma.com]	$3,286	$689.1	**Lunesta** [517]
42	**Grifols** **Barcelona, Spain** [grifols.com]	$3,245	$163.5	**Gamunex IGIV** [1,105]
43	**Hospira** **Lake Forest, Illinois** [hospira.com]	$2,759	$301.7	**Precedex** [288]
44	**Aspen Pharmacare** **Durban, South Africa** [aspenpharma.com]	$2,710	$1.6	**N/A**
45	**Lundbeck** **Copenhagen, Denmark** [lundbeck.com]	$2,431	$511.6	**Cipralex** [1,057]
46	**STADA Arzneimittel** **Bad Vilbel, Germany** [stada.de]	$2,407	$74.2	**Apokyn** [58]
47	**Kyowa Hakko Kirin** **Tokyo, Japan** [kyowa-kirin-pharma.com]	$2,334	$435.7	**Nesp** [559]
48	**Sun Pharmaceutical Industries** **Mumbai, India** [sunpharma.com]	$2,311	$175.3	**Levulan Kerastick Topical** [61]
49	**Purdue Pharma** **Stamford, Connecticut** [purduepharma.com]	$2,217	$456.1	**OxyContin** [1,900]
50	**Ranbaxy Laboratories** **Haryana, India** [ranbaxy.com]	$2,199	$108.0	**Atorvastatin** [210]

Sources: Company financial statements, SEC 10k reports, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys.

How Digital Medicine Can Pinpoint Dosing Regimens to Optimize Drug Efficacy and Safety

ON-DEMAND WEBCAST

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EVENT OVERVIEW:

Identifying the optimum dosing regimen for recommended use remains one of the more difficult tasks in pharmaceutical development, with major therapeutic and economic consequences. According to Nature Reviews | Drug Discovery, 56% of Phase II-III failures from 2011-2012 were caused by lack of efficacy, and 22% caused by safety issues.

Today, advances in digital medicine and electronic data capture enable accurate and timely insight into medication adherence during a clinical trial—helping to determine the optimum range between the dose-response curves for both desirable drug effect and unwanted drug toxicity.

Attend this webcast to discover how you can:

- Directly confirm when, what type and how much medication was actually ingested, removing assumptions enabling better Phase III dosing decisions on efficacy and toxicity
- Obtain clean, clear medication ingestion data automatically and within hours directly from patients to an EDC system, exactly as lab data is collected
- Eliminate imprecise and manual processes for collecting adherence data such as pill counts and questionnaires
- Reduce monitoring costs while enabling critical distinctions between non-adherence and non-response

The result of this FDA- and EMA-approved approach is greater confidence in minimum effective exposure-response, and greater confidence in maximum safe exposure-response—increasing clinical study speed, efficiency and accuracy.

Key Learning Objectives:

- Discover how the integration of digital medicine with electronic data capture (EDC) systems creates a unique platform for capturing accurate and timely medication ingestion data
- Review how this adherence insight can remove potential for patient bias in self-reported compliance
- Explore the range of ingestion data reporting that turns data into actionable information for rapid go/no-go decisions, mid-stream study adjustments, monitoring improvements, and more

For questions, contact Sara Barschdorf at sbarschdorf@advanstar.com

Presenters:

Dr. Markus Christen
Senior Vice President, Global Head of Development
Proteus Digital Health

James Streeter
Senior Director, Life Sciences Product Strategy
Oracles Health Sciences

Who Should Attend:

- Anyone involved in R&D Strategy
- Heads of R&D
- VP/Directors/Managers Clinical Development
- VP/Directors/Managers Clinical Operations
- Therapeutic Area Head
- Innovations Teams
- Clinical Pharmacology

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and Mexico. All other remaining countries outside the BRIC and the other 17 Pharmerging countries are grouped together as ROW. This group includes the smaller European countries as well as Canada and Australia.

If we look specifically at the companies in the Pharma 50 list, we see that the increase in specialty pharmaceutical sales for US, EU5, and Japan is primarily driven by these top companies in global sales of Rx products (see Figure 2 on page 30). In these markets, there is already a high level of specialty products usage, aided by a well-established infrastructure of specialist facilities and physicians to treat and prescribe these medicines.

There is also a strong increase in their usage likely due to the large investments companies have placed in securing access for specialty medicines in these markets, an increased aging population in these countries, and societal willingness and ability to pay for treatments for complex—often rare— diseases.

The increasing spend on specialty drugs for the Pharmerging markets, including BRICMT and Tier 3, is relatively smaller than the other markets, likely reflecting a higher cost of therapy relative to income, higher levels of cost borne directly by patients, and a relatively younger patient population that carries a greater need for products focused on primary care.

Although companies have been placing significant emphasis on expanding their specialty franchise into these areas, they still face challenges around drug awareness, availability, and affordability. This has slowed the transition to specialty and led to smaller changes in the product mix than in the US, EU5, and Japan. The significant increase in specialty products within ROW also reflects the investments being made by Pharma 50 companies in smaller markets outside of the G7 that have established infrastructure for these types of products (e.g., in Scandinavia, East Europe, Australia, and Canada).

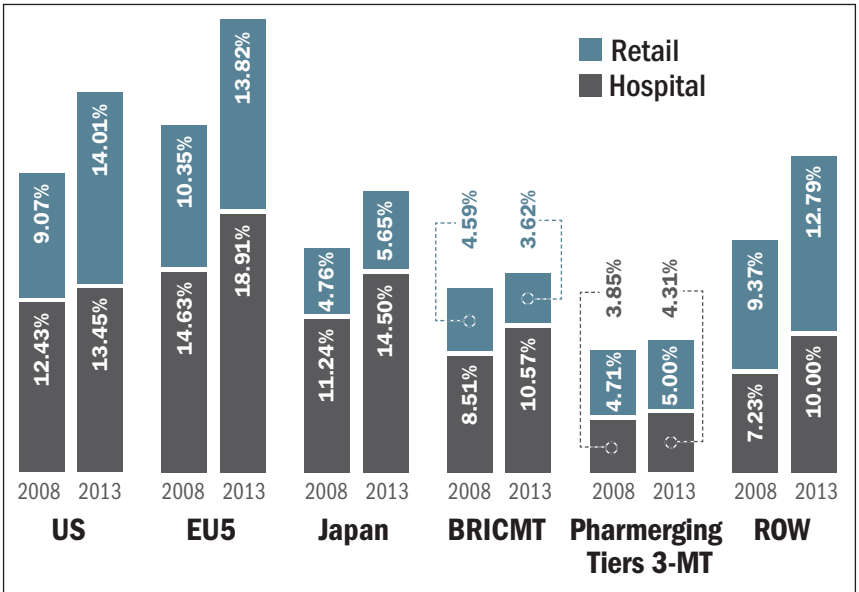

Figure 3: Specialty market percent of total sales by channel (Data: IMS)

Channel growth

The sale of specialty products historically has been through hospital or specialized care settings that can provide the infrastructure required for the administration of biologically complex products. With advances in technology and new classes of drugs, we have seen a trend towards increased sales through the retail sector. Existing products also have been recast in formulations that are more amenable to use in the retail sector. Examples of these innovations include oral administration rather than injection for rheumatoid arthritis, multiple sclerosis, hepatitis C virus, cancer, and a number of orphan-drug diseases; more robust formulations that have less need for special storage requirements, like self-injectable pen devices; or subcutaneous formulations, like Roche's Rituxan, which can be administered by health professionals outside of a hospital or home care setting.

The growth of this retail market is most pronounced in the US (see Figure 3). In 2008, if we break down the 21.5% of specialty from Figure 1, we see that 12.4% of total pharma products in terms of value were specialty products administered through the hospital setting and about 9.1% through the retail setting. By 2013, the hospital setting remained relatively stable at 13% whereas the retail setting increased to 14%.

For the US, this large movement of value through retail channels sets up newer challenges for pharmacy benefit managers who are now saddled with larger payouts for products which they were not necessarily having to reimburse before. This means that specialty products are now on the radar screen for payers, suggesting that increased sensitivity to cost among the reimbursement community will have an as yet unquantifiable impact on future rates of sales growth, in a segment where price has rarely been a contentious issue.

In the EU5, there seems to be a higher proportion of specialty product usage than in the US, and a rise in both hospital and retail sales. This is being driven by adoption of newer therapies under the single-payer structure of these markets, and the proportional increase is amplified by the declines in spending on traditional medicines related to patent expiries, widespread take up of generics, and pricing and reimbursement controls. This comparison to the US may be impacted by the fact that sales are based on the ex-manufacturer invoice price,

i am insightful

It took 10 years to complete my clinical training. Hardly surprising that it can be difficult to get your head around the area if you're not familiar with it. That's why I enjoy working with our team of specialists, because I understand what they need me to. And that makes it easy for me to translate our experience into useful insights for you.

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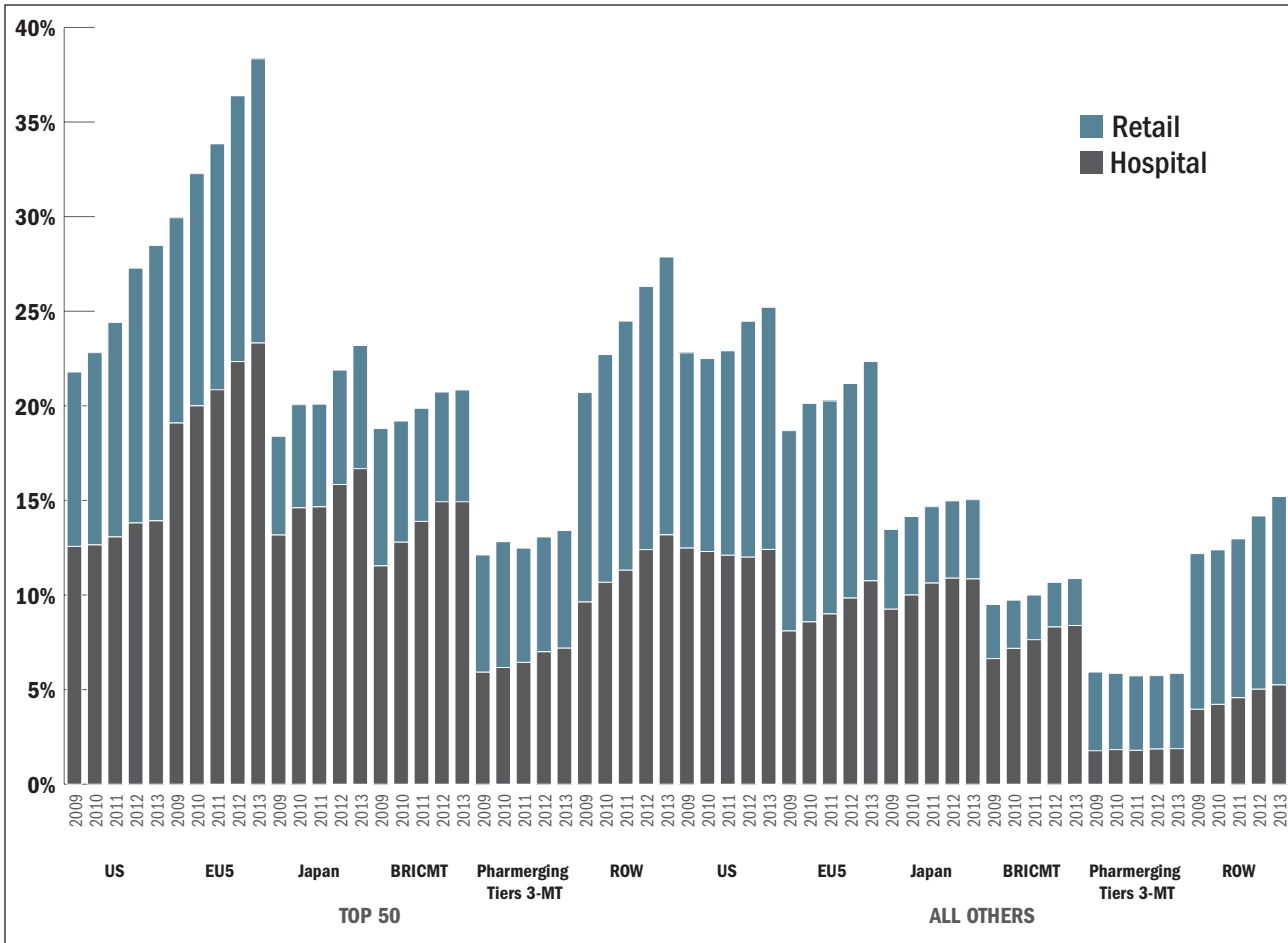

Figure 4: Specialty market percent of total sales by channel and by Pharma 50 past 5 years (Data: IMS)

since discounting is more prevalent in the EU. For Japan, the retail sector has not increased significantly, presenting an opposite picture to the US. This is largely because complex therapies continue to be administered in hospitals.

We would expect that retail sales for specialty in the BRICMT and Tier 3 countries would not increase significantly given the traditional infrastructure difficulties of selling these products outside of the hospital setting; in fact, the share of specialty medicines in retail in BRICMT has actually declined over the past five years.

When looking at the Pharma 50 companies sales in specialty over the past year by channel, we can see the accelerated pace of growth in this market (See Figure 4). In almost every geography, there has been an increasing surge in specialty products driven mostly by the Pharma 50 companies. This effect is most pronounced in the EU5 and US. It is also notable that the EU5 share of sales that is specialty exceeds that of the US, as does the growth rate for top 50 companies, but this comparison may also be impacted by the use of ex-manufacturer invoice price. Also interesting is the increasing gap between Japan and the BRICMT markets in their specialty share of overall spending, as Japan has encouraged greater usage of specialty products, especially in cancer and autoimmune diseases.

Therapeutic area growth

When looking at the top therapeutic areas in the specialty market, we see that the top 7 out of 22 categories usually account for anywhere from 70% to 80% of the value depending on the geography (See Figure 5 on facing page). From 2008-2013, these therapy areas have stayed a relatively stable percent of value within the geographies, except for the US, where they increased from 72% to 76% of total US sales of specialty products.

The leading specialty categories are oncology, autoimmune (including treatments for rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis), HIV, multiple sclerosis, erythropoietins, hematopoietic growth factors (e.g., Neupogen or Neulasta), and hepatitis C treatments. This group of products represents the most commonly used, and often most expensive specialty medicines. They also represent a strong level of recent innovation. For example, the US and EU5 have seen

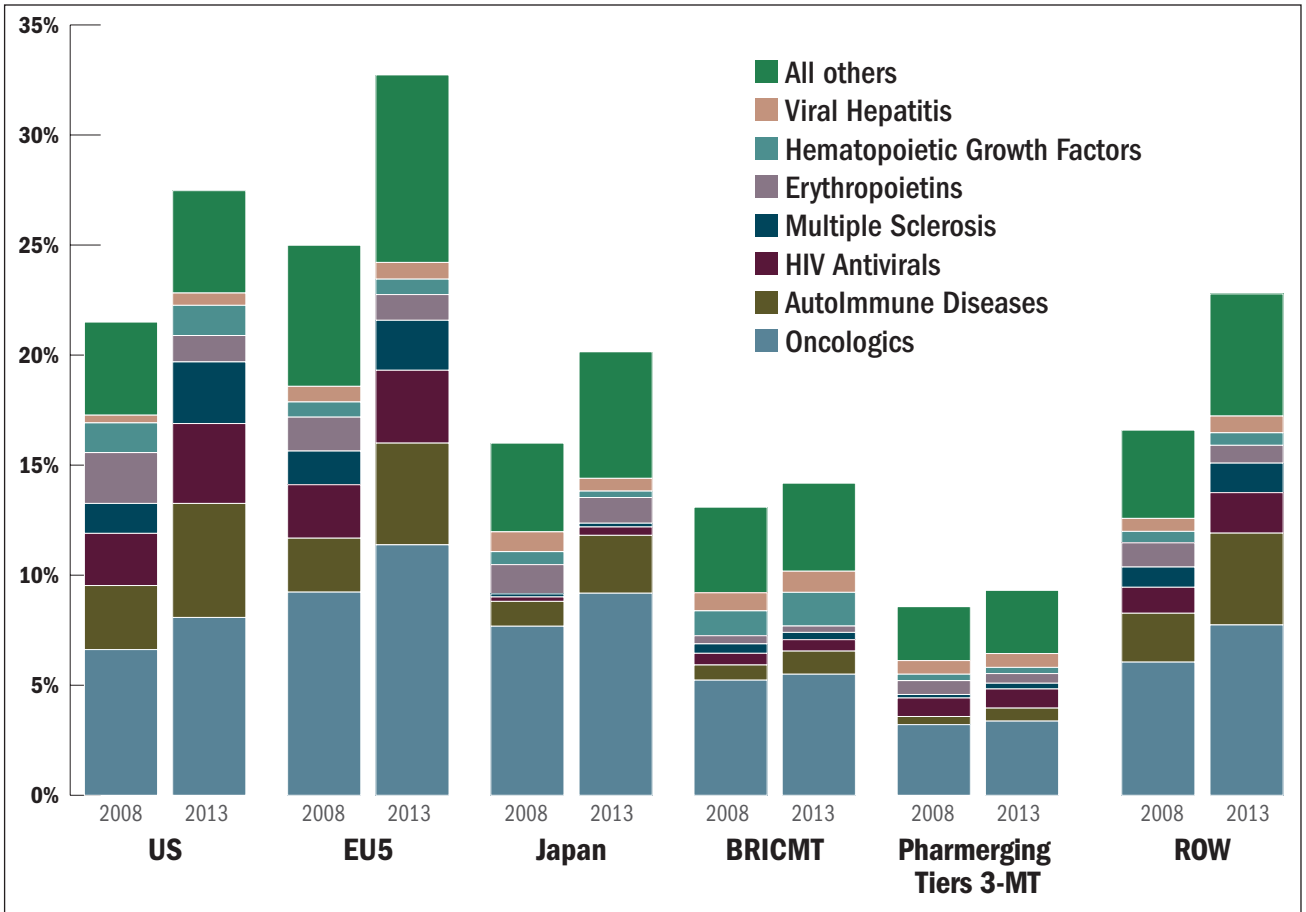

Figure 5: Specialty market percent of total sales by therapeutic area (Data: IMS)

growth in oncology, autoimmune, MS, HIV, and hepatitis C categories, driven by the availability of newer medicines. Of course, the wide range in share of sales for the different therapy areas across geographies highlights differing priorities for medicine spending, along with differing disease prevalence and affordability for high-cost medicines.

Conclusion

The value and volume of specialty products is increasing substantially across all geographies, and this is being driven by the increased development of specialty medicines across a range of diseases. This is a positive indicator that innovation in medicines is continuing to expand the societal and economic benefits from investments in medical progress. It may be that as diseases addressed by these products receive higher recognition by societies and governments, the costs will be more easily shared across geographies and among newer stakeholders.

It is also critical to note that growth of the specialty market can be linked to rising global incomes. For Pharmerging markets, this will continue to be true in the future. The rise and empowerment of the middle class, increased initiatives by pharmaceutical companies in partnering for the expedited delivery of healthcare, and greater private insurance to augment government healthcare funding will all contribute to patients gaining greater access to medicines.

The growing specialty market is a ripe opportunity for companies that are well-established in the field and have considerable marketing presence. A key factor for success of these companies will be to develop innovative solutions that distribute costs of these therapies between manufacturers, payers, and patients in order to achieve broader access in and between geographies and across patient populations. The challenges are many, however, and are not limited to protecting IP in emerging markets or addressing payer resistance to prices for innovative products in the G7 countries. This is especially true when access decisions and pricing negotiations in one country have a trickle-across effect on others.

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The Urge to Merge:

Lessons from History's Storyboard

By Cliff Kalb

The major pressures hindering pharmaceutical industry success have not changed—payer constraints on drug costs, R&D productivity, an increasingly risk-averse regulatory climate, generic encroachment, and negative public perceptions linked to reputation. The controversial kickoff of the Affordable Care Act in the pivotal US market adds a new dimension to an already complex environment. It follows that the appropriate industry response to these challenges has not changed much either: future industry growth will depend on its ability to develop and successfully market innovative new products while adapting to the rapid transformation in the way healthcare is financed and delivered.

Looking at the latest rendition of the Pharma 50, prescription drug revenue rankings for the top 10 major global players in 2013 show some modest shifts among the leaders, but no change in the members of the group. While Novartis has displaced Pfizer for the top spot, both of these firms have already engaged in deal-making in 2014, which could reverse the pattern again.

To successfully access innovative products in areas of high unmet medical need and sustain revenue growth, many firms have chosen to acquire or merge with competitors. In 2009, the industry changed dramatically when three high-profile mega-mergers occurred—Pfizer's purchase of Wyeth, Merck's reverse acquisition of Schering-Plough, and Roche's buyout of the remainder of Genentech it didn't already own. Mega–merger activity in the industry is not new. For example, Novartis was formed in 1996 when Sandoz merged with Ciba-Geigy, which itself was the product of a merger in 1970. Today's Sanofi is actually an entity that represents a collective of some 11 companies that had been previously independent. A 22-year illustrative history of industry merger activity from 1989-2011 is shown in the chart on facing page.

All mergers, regardless of industry, are driven by the need to sustain competitive advantage. The rationale for pharmaceutical industry merger activity over the past two decades has been the perceived need for increased economies of scale, improved R&D productivity, access to new technologies or geographies, and increased exposure to patent loss and generic competition. The 2009 mega-mergers anticipated an extraordinary wave of blockbuster expirations in the 2011/12 window, including Pfizer's Lipitor, GSK's Advair, AstraZeneca's Seroquel, and Sanofi's Plavix. However, developing and rapidly ramping up new drugs to replace the lost revenue—particularly in the US—has proven difficult.

During the most recent five-year period from 2010-2014, the mergers did not rise as high in public notice as some of those of the past. This recent window included such deals as Abbott /Solvay, Takeda/Nycomed, Teva/Cephalon, Gilead/Pharmasset, Valeant/Bausch&Lomb, Perrigo/Elan, and Actavis/Forest, just to name a few. These transactions didn't necessarily carry the lasting headline impact as those among the top-ten players, but were just as transformational for these firms, albeit on a more modest financial scale.

However, increased scale alone is not a sustainable solution to industry woes. Mergers in the pharmaceutical space have primarily been short-term efforts to realize economies of scale, fill revenue gaps, and buy time for the pipeline to produce desired organic growth. There is little evidence that the temporary increases in market share and market cap that result from these deals results in sustainable leadership or enhanced shareholder value. On the other hand, there is extensive evidence of massive job loss, facility closings, and a decrease in the commitment to R&D, marketing, and production. For companies who take the "merge to grow" strategic path, real productivity gains may be an illusion. Barriers include:

- Inefficiencies involved in restructuring.
- Conflict of cultures/decision-making styles.

- Distraction and loss of external focus during integration.
- Demotivated employees resulting in loss of productivity (fear of layoffs).
- Loss of corporate brand equity as trusted firms disappear from the landscape.

Taxation is an aspect of merger activity that did not have a high public policy profile until today's recent pending proposals. Globalization and growth in emerging markets is another under-appreciated industry dynamic that occurred over the past 25 years. This trend has generated billions in off-shore profits for US-based multinationals. These funds have remained overseas as repatriation to the US would result in taxation at US rates, now the highest in the developed world. Several smaller deals have already addressed this concern by redomiciling corporate headquarters to a jurisdiction with more attractive tax rates such as Ireland and Canada.

At least two of the current prospective merger proposals, Pfizer/AstraZeneca and Valeant/Allergan, can be added to the list of those attempting to capitalize on this "tax-inversion" benefit. The Pfizer deal, however, is a $100-billion-plus-proposed transaction. This vast scale has raised the issue to a level where governments are taking notice. At least in the UK, hearings have been held to explore the long-term impact of the proposal on employment, R&D innovation, and national interest. This saga is still ongoing and has important policy implications for needed action on US corporate tax reform for all US multinationals.

While the merger route to growth has recently brought this new financial dimension to light, several other deals have been announced in 2014 that illustrate a very different strategy. Central to this alternate approach is portfolio optimization. After a thorough review of its portfolio of business units, Novartis bought GSK's oncology business and sold its vaccine unit to GSK. While each firm had competing stakes before in these businesses, these deals strengthen their respective leadership roles in therapy areas where they remain, and narrowed their focus. A JV was created in OTC products between them. Apparently, both management teams viewed OTCs as core to their future, and this arrangement will broaden the OTC portfolio. Novartis also sold its animal health business to Lilly, enabling Lilly to become the No. 2 global player in this area. Another example of portfolio management is Merck's recent sale of its OTC business to Bayer, and the creation of a JV with Bayer in cardiovasculars.

These sets of transactions seem far more pragmatic than the "merge to grow" strategy. In each case, the firms carefully studied their portfolios and those of competition. They identified areas of internal weakness that would strengthen a partner and vice versa, and acted prudently. While one can question the valuations of these businesses, the portfolio optimization strategy of these players clearly appears to be win-win, and far less disruptive than the merger path and the integration difficulties that follow. It is my hope that this sensible type of dealmaking behavior becomes more prevalent in the future.

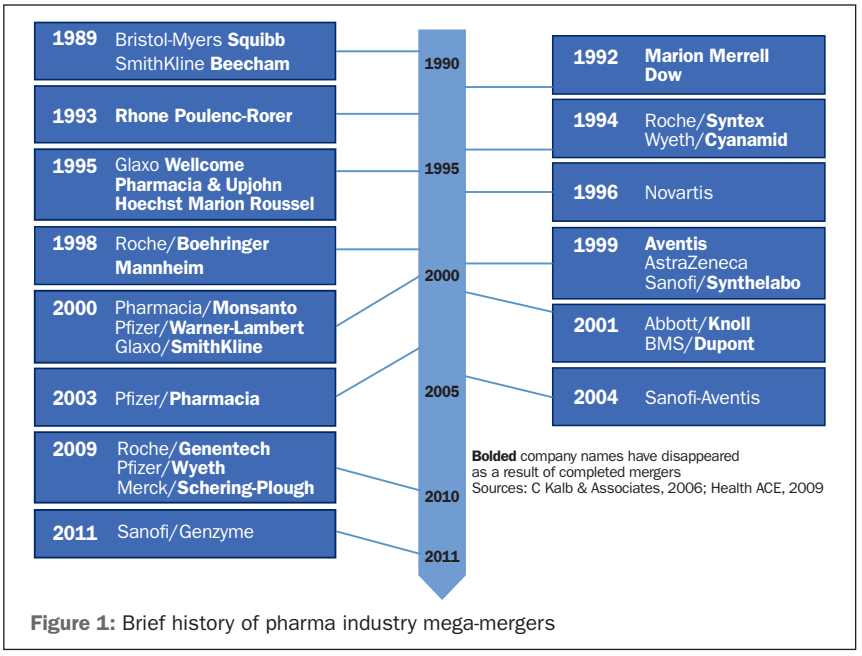

Figure 1: Brief history of pharma industry mega-mergers

It is rational to ask if the next phase of industry evolution might be a swing back toward "de-merging?" The spinout of AbbVie and Baxter's pharmaceuticals unit are examples of unlocking hidden shareholder value in pharma businesses hidden within larger health care conglomerates. The law of large numbers makes it very difficult to grow the top line for massive centralized pharma businesses. This seems to be driving Pfizer, GSK, Merck, AstraZeneca, and others to consider breaking up their large pharma businesses into separate units, or selling off groups of older products to secure additional cash for strategic investments in their chosen areas of strength. Perhaps the business model pendulum could benefit from a swing in the other direction? Like all other aspects of the human condition, the life of business is destined to repeat itself—it may cause a shock, but it is not new. PE

Cliff Kalb is President of Kalb & Associates and a member of *Pharm Exec*'s Editorial Advisory Board. He can be reached at ckalb55205@aol.com.


Photo: Thinkstock

Surviving the Price Wars in Emerging Markets: Three Myths and Three Lessons

Ways that big Pharma players can avoid a corrosive battle of attrition with local competitors and instead obtain the long-term goal of a stable pricing environment.

By Ken Genenz, Cova López-Sors, and Rafael Alencar

In ancient Greece, King Pyrrhus of Epirus fought and defeated the Roman army twice during what is now known as the Pyrrhic wars. However, victory was achieved at an ultimately unsustainable cost because of the high burden of casualties. The story is an apt comparison to the far more prosaic challenge of building a pricing strategy in today's fast-changing emerging markets, where companies are enmeshed in ruinous price wars that destroy value and profits for all parties involved.

One recent example, from 2012, involves one of the top 10 manufacturers in Brazil. The company, a leading MNC, wanted to preserve its market leadership and was under pressure from the distribution chain. Discounts on the list prices of its products had reached as high as 95% below those of its major competitors. Coupled with an expected increase in demand ahead of a tax increase, the result was that products from the company flooded the distribution channels. This led to a steep loss in selling power, with many products returned to the manufacturer near their expiration date. And guess who had to foot the bill?

Overall, this strategy led to losses of several hundred million dollars for the company in only one quarter. It was a figure higher than the earning loss from the worldwide patent expiration of one of the multinational company's key blockbuster products. The predicament it faces in Brazil is unfortunately all too familiar to the many manufacturers that strive to beat the performance norm for emerging markets at all costs.

Cash is king

Regardless of recent economic turmoil, key emerging markets remain a significant source of growth for drug companies. While some MNCs haven't fulfilled their ambitious growth targets in emerging markets, Bayer Healthcare and Sanofi are succeeding; emerging markets already account for 30% of their revenues. According to IMS Health, retail sales of pharmaceuticals in Brazil surpassed those of key developed markets like Canada and the UK in 2010 and continue growing at double-digit rates. However, one important characteristic of emerging markets is that most business originates from patients paying out-of-pocket, as opposed to sales funded by the government or private payers, as is common in developed markets. This especially holds true for chronic conditions retail drugs and much less for high-cost drugs such as biologics.

In India, more than 95% of the pharmaceutical expenditure is out-of-pocket, while in China and Brazil patients pay 65% and 80% of the cost of medicines out-of-pocket, respectively. These high rates are only in part due to the limited involvement of public payers in overall health spending. A more important factor is the growth of an emerging middle class with discretionary income that can be spent on products that are not funded through third-party sources.

Pricing out-of-pocket: A different game

Many companies are struggling to maximize their profitability in the out-of-pocket market. There are some important peculiarities that are often overlooked, but need to be considered when designing a strategy for this segment.

- **The patient is the main decision-maker:** Unlike what happens in reimbursed markets, mere clinical evidence is insufficient to support the value of the product and trigger the buying decision. Apart from perceived clinical benefits, patients will consider other perceptual attributes like the reputation of the manufacturer or even recommendations from family and friends. Looking at the list of top-selling drugs in China, for example, most of the products from MNCs lost patent protection years ago, yet still achieve significant sales. In this sense, the behavior of the patient is more similar to what is seen in the consumer goods industry, where products with a strong perceived brand can avoid comparisons based only on price. More importantly, trust in the brand is vital in the many emerging markets where drug quality and counterfeit products are real issues of concern.
- **Importance of stakeholders in distribution channels:** Distribution channels involve many players, but sales tend to originate from only a few key accounts. These are typically large retailers with the negotiating power to force manufacturers to offer steep discounts. In Brazil, many manufacturers see 70% or more of their sales coming from just two retail chains.
- **Lack of regulated margins:** Unlike in many mature markets, retail margins are not fixed by law in many emerging markets. Net prices can be set freely below maximum prices.
- **Fierce competition from established local generics:** Most of the growth in emerging markets has been captured by local companies specializing in generics. Generic penetration is very strong in emerging markets. In India, for instance, the volume uptake of generics is more than 99%. Many of these manufacturers compete aggressively on price based on low productions costs in order to gain market share. Nevertheless, some of the local companies have managed to stay out of this race to the bottom and are very profitable; the Brazilian company Aché is an example.

The drastic price drops that occur as a consequence of competitive price wars have a destructive impact on the entire market for medicines.

Deconstructing myths

The drastic price drops that occur as a consequence of competitive price wars have a destructive impact on the entire market for medicines. All the companies involved—manufacturers and distributors—see their margins decrease significantly. What is worse, most will face difficulties recovering their lost margins. The destruction is in many ways unnecessary because companies will often engage in price wars based on false assumptions—we call them myths:

- **1st myth: "Low prices will drive volume and therefore profit"**

  Guided by an appreciation of pure volume-based incentives, management may think a price decrease will increase demand for their products. However, such a cut has two consequences: A volume increase and a margin decrease. Therefore, the total impact on profits depends on the strength of the volume increase, which is determined by the elasticity of the price. Price elasticity—which is a function of the consumer's

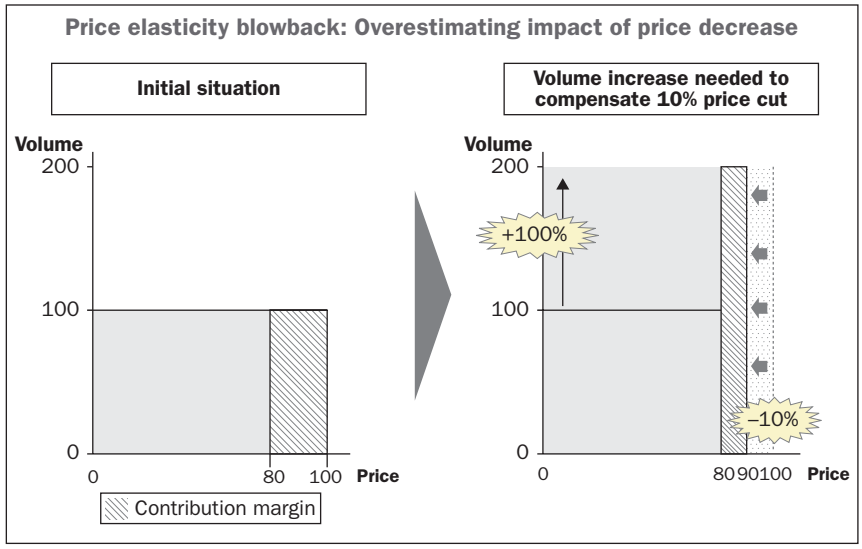

Figure 1: The above depicts an outcome scenario where a manufacturer with a gross margin of 20% decides to decrease its price by 10%.

response—predicts how much demand will change when prices change.

According to our latest research work on global pricing, most managers tend to overestimate the positive impact of a price decrease on volumes, while they underestimate the negative impact on margins. Figure 1 (above) shows a scenario where a manufacturer with a gross margin of 20% decides to decrease its price by 10%. In order to maintain the same profit, the manufacturer would have to double the sales it had before the price decrease. This would require a price elasticity of -10 (i.e., volumes need to increase 10 times the price decrease). This is much higher than the elasticity of innovative branded products, which is typically between -0.2 and -0.7. Even generics do typically not have a price elasticity exceeding 2.5. The manufacturer, in this example, is, therefore, very likely to have a lower profit after the price decrease.

» **2nd myth: "Our competitor started the war, so we should react by lowering our prices"**

Companies hardly ever admit or realize that they started a price war. According to Simon-Kucher's Global Pricing study, when managers were asked who started the price war, almost 90% of them answered: "It was the competitor." Some companies truly believe their business is like a battlefield, where the competitor must be destroyed. However, war and business have two key differences: (1) All wars end at some point, but in a free market, there will always be competition; and (2) There are no customers in the battlefield, so companies should focus on responding to customer needs, not destroying the competitor.

The profit loss caused by a price decrease is usually greater than the loss caused by a decrease in market share. In addition, reacting to a price decrease of the competitor with a similar price cut typically starts a vicious circle of price cuts, since the competitor will try to maintain the original price difference. For this reason, the best possible reaction when the competitor lowers prices is to not change prices. In the end, lowering prices only intensifies the price war with disastrous consequences for the profits of all manufacturers involved.

» **3rd myth: "When the war ends, we will increase the prices"**

Most managers would agree that a price increase is never easy. There are three facts that support that this also holds true for price increases after price wars.

First, competitors always endure the attack for a longer time than what was initially estimated, making it difficult to end the war. Price wars always last more and cost more money than expected. There is never a "winner," as there will always be competitors in the market. If competitors vanish, it is only because the margins are so low that it is no longer worth competing in the market.

Second, it is very difficult to increase prices to patients used to a low-price level, especially when price is the sole attribute manufacturers focus on.

Third, a price increase will also increase margins, making the market attractive again to competitors, which means a new war may loom soon.

Brazil's biggest maker of generic drugs and hygiene products, Hypermarcas, sets a real-life example on how to exit from a price war. In 2011, Hypermarcas was immersed in a price war against other competitors by offering big discounts and granting favorable payment conditions to distributors to gain market share. As its profit margins declined, Hypermarcas made a difficult decision: reducing discounts and shortening payment terms. Some key clients suspended their orders for several months; however, as soon as they ran out of stock, they placed new orders. Following a loss of $50 million in 2011, Hypermarcas posted a net profit of $100 million in 2012.

Is there a silver bullet to end price wars?

It is easy to deconstruct myths about pricing, but, unfortunately, there is no silver bullet to end all price wars and increase profitability. Pricing is a key internal process that companies need to address holistically, from strategy development to price setting to price execution. However, we can outline three action items a company should consider to minimize the risk of price wars:

» **Quantify the impact before lowering the price:** Before lowering prices by giving discounts or price promotions, every manufacturer must be able to answer these three questions:

1. How much more volume would need to be sold to reach at least the same level of profits as before the price decrease? This can be easily calculated with the current gross margin.

2. Is price elasticity high enough to achieve those volumes? As we have seen, if the required price elasticity is far from the elasticities typically seen in the market segment, is it realistic to believe such volume increase is possible?

3. How would the volumes and profits be affected if the competitors react and match the price decrease? Never underestimate the ability of competitors to further undercut their prices.

Making a price decision without a clear answer to these questions is very dangerous. When competitors lower their prices, many managers follow suit without considering the consequences on profits in the short and the long run.

» **Don't give away discounts without compensating for it:** Sales reps or account managers frequently offer unnecessary discounts that undermine the company's profitability, as a result of the lack of a clear commercial policy. In many cases, the best conditions are granted to the worst clients. Very often, an analysis of discount structures surprisingly shows no correlation between the discount to a client and the volume or other variables related to the importance of the client (see Figure 2 above).

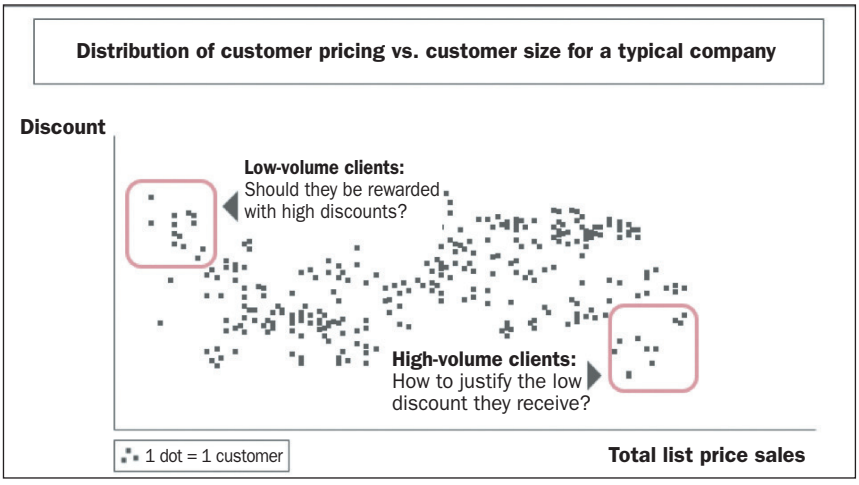

Figure 2: An analysis of discount structures shows no correlation between the discount to a client and the volume or other variables related to the importance of the client.

Pricing is a key internal process that companies need to address holistically, from strategy development to price setting to price execution.

Another useful exercise is the analysis of the price waterfall that is illustrated in Figure 3 (see page 42). It shows what happens between the list price and the net price for each customer. Startlingly, the real net price per customer is not even available on a per-product basis in many cases. The level and structure of discounts is often not linked to the strategic importance of the different customer segments.

Typically, a redesigned pricing process to consistently reward strategically important customers and limit discounts for underperforming clients can increase return on sales by 200 to 500 basis points. Optimizing trade terms is a complex task, but the resulting optimal discount structure may actually be very simple. Some of the most profitable pharmaceutical companies in Brazil are a few local companies. They grant discounts based on a commercial policy with only a few product categories and limit discount levels to an absolute minimum.

Rewarding good customers with higher discounts can be dangerous, as it can foster concentration of buying power, which can then be turned against the manufacturer that offers them.

An example of a company that successfully addressed ruinous competition between its customers is AstraZeneca in Mexico. In 2009, the company came up with a disruptive solution to put an end to increasing demands for discounts from competing distributors. A uniform retail price across Mexico

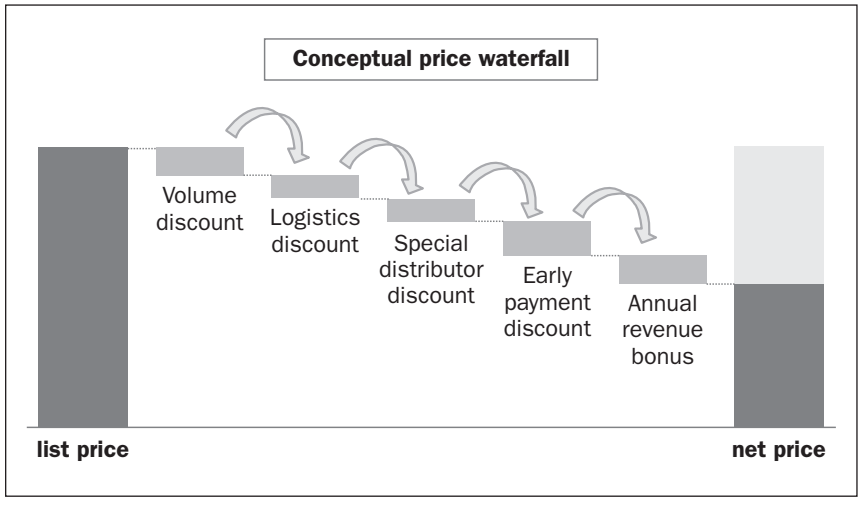

Figure 3: Illustrates what happens between the list price and the net price for each customer.

was introduced, a move that favored small pharmacies and limited further concentration of buying power. Exclusive distributors were paid a fee for service instead of working based on margins. Wal-Mart was initially lost as a client, but now most of the MNC pharmaceutical companies have switched to this business model as well. This example also illustrates the importance of seeking legal guidance before making any pricing decision, as implementing a similar solution in other markets requires considering local anti-trust regulations.

» **Understand different patient segments and choose your battles:** Significant income inequalities in emerging markets lead to different segments of patients with a broad range in terms of willingness to pay. Identifying these segments is crucial in defining the product and price strategy of the portfolio. For example, in China, a population segment of 13 million has an income of at least $25,000 per year; their willingness to pay is very different from the 400 million that earn $5,000 per year or less. If manufacturers want to reach the bottom of the pyramid, they need to assess the profit impact of potentially significant discounts on products currently serving the top of the pyramid.

A well-executed price differentiation strategy will often yield a superior result compared to an across-the-board cut of products currently serving the top of the pyramid.

These income inequalities may justify significant price reductions that are typically not advised in mature markets. A price cut that allows a manufacturer currently focusing on the top of the pyramid in China to reach out to the middle of the pyramid by offering a moderate discount may pay off. However, this still requires doing the math on the volume implications of the price change, which may vary a lot by product.

Within this context, it may be necessary to go beyond factors related to volumes and revenues and look to other considerations such as policy and corporate social responsibility, which will ultimately contribute to the bottom line. For example, from a short-term financial perspective, the optimal strategy for a drug may be to set a high price, reaching the very top of the income pyramid only. However, this may lead to reactions by advocacy groups, which could eventually trigger government actions such as price controls or even compulsory patents, with a negative impact on the bottom line.

A potential strategy to target the different segments of the pyramid is to offer a broad portfolio of clearly differentiated products serving different patient segments. A well-executed price differentiation strategy will often yield a superior result compared to an across-the-board cut of products currently serving the top of the pyramid.

The end game: Peace instead of Victory

By applying these three rules, manufacturers will not win price wars, but will be one step closer to not even starting them—or at least knowing how to get out of them. Pyrrhus, the King of Epirus exclaimed after his second victory: "If we are victorious in one more battle, we shall be utterly ruined." With this in mind, drug manufacturers in emerging markets will hopefully no longer fight battles that they can't win. PE

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Take as Directed: From Force to Finesse in Promoting Adherence

Three important players in the healthcare delivery system—payers, pharmacy, and pharma—say patient education and engagement are the keys to better drug adherence rates. Patients agree, as long as education and engagement translates into convenient and affordable access to therapy.

By Ben Comer

The figures vary a little, but the consensus hasn't changed much in the last decade: non-adherence, in the US alone, is at least a $100-billion-a-year problem, with patients getting sicker, showing up in the ER, or getting an operation that might have been avoided if they'd only taken their meds according to doctor's orders. Of all avoidable US healthcare costs, non-adherence is by far the largest, reports IMS Health (see chart on facing page).

Depending on therapeutic area, patient characteristics, insurance coverage, and other factors, estimated non-adherence rates among patients range from 25% to 50% in the US, where nearly half of all adults have at least one chronic disease, according to Centers for Disease Control (CDC). An estimated 10% of hospitalizations in older adults may be attributable to skipping doses, or failing to pick up drug refills.

Everyone knows the statistics but the problem remains despite multichannel disease awareness efforts, new mobile apps, digital tools for tracking health behavior and insurance plan or pharmacy incentives. Efforts to make medicine participatory—instead of rigidly paternalistic—haven't had an enormous impact on non-adherence to date. That's because the choice to take a pill or an injection, in the outpatient setting, is an utterly personal decision—it's based on a panoply of variables, from cost of therapy and the potential for side effects (and how they conflict with day-to-day obligations), to physician trust and the level of comprehension related to risks associated with non-adherence.

It also has to do with plain old forgetfulness, inconvenience, and differing individual priorities. For many patients, collaboration in the context of healthcare decision-making sounds like more work and more effort at a time when jobs and family already compete for any spare time left during the day or night. And yet, "most of what determines [health] outcomes happens outside of the doctor's office," said Farzad Mostashari, a visiting fellow at the Brookings Institution and former National Coordinator for Health Information Technology at HHS, during the SAS Health Analytics Executive Conference in North Carolina last month. What is Mostashari's prescription? "Reduce friction and increase services to promote loyalty." If being adherent to a medication becomes easier than not being adherent, the statistics may finally take a turn.

Greasing the wheels

During a roundtable discussion at the mHealth Summit last December, Vera Rulon, director of external medical communications at Pfizer, recalls sitting next to a diabetes patient who said she "didn't want to be bothered" with a medication regimen, to the extent possible. This patient "wanted something that monitors blood sugar, gives you insulin when you need it or at least alerts you when you need to do something, in a seamless and transparent way," says Rulon. Providing a seamless experience means understanding more than just the nature of a given disease, and a drug's product attributes. It also requires an understanding of the patient, and his or her real-world environment.

"For this particular medication, you do need to look at these factors, and this is what may have an impact on a person's response," for example, says Rulon. "Physicians need to be sensitive to a patient's perspective…building a rapport and trust, and sharing in the decision-making process helps get buy-in for patients to do what they need to do to help themselves."

In addition to actual products that make sustained adherence to therapy an easier pill to swallow are programs that make prescription drugs easier to get. Payers are often seen as the primary barrier to quick and convenient drug access, since a growing number of prescriptions are written for expensive specialty products that require prior authorization, step therapy, or higher copays or coinsurance to obtain. Patients taking biologics for chronic disease are often forced to play the same pharmacy counter game of phone tag with insurance companies and physicians every few months, to keep the refills coming.

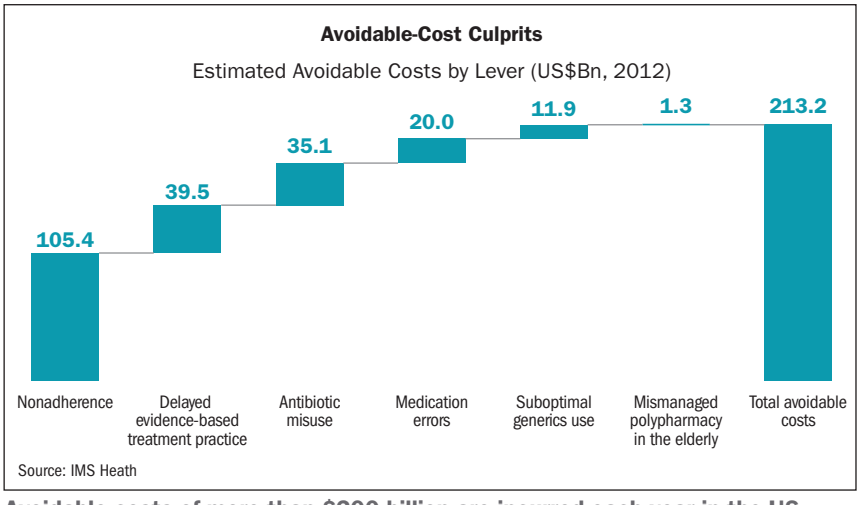
But insurance providers are partnering with pharmacy benefits managers (PBMs) and even health information companies like WebMD to provide a more convenient way for patients to request and fill prescriptions. Insurers like United Health and BlueCross Blue Shield are experimenting with premium discounts in employer health plans for those patients who can document certain healthy activities, including medi-

cation adherence. Pharmacies, too, are launching new service offerings to promote better adherence rates and to build loyalty with patients.

Kaiser Permanente's integrated model puts it in a unique position to combine insights across the payer and pharmacy verticals. Terhilda Garrido, VP of health IT transformation and analytics at Kaiser, says patients can digitally access their own personal health records without having to enter any data themselves, and can also request refills, and even ask for mail order and pay with a credit card. Garrido says one of Kaiser's basic models is to "make the right thing easy to do," which in this case means getting prescription refills to patients with minimal effort. Like an Amazon.com purchase, Kaiser's patients can sign on and click to get a product order—in this case a medication refill—delivered by mail. "I've actually used it myself," says Garrido. "I've studied this stuff, but when you actually use [a refill delivery program], you think, 'Wow, this is pretty great.'"

Since online refill requests for prescription mail order are routed through one of Kaiser's fulfillment houses (which is "much more automated than the local facility at the medical center or clinic"), it's a lower cost-per-script filling rate, says Garrido. "So, we're thrilled about some of the advantages that being on the Internet is giving to our patients."

Kaiser invested $4 million in electronic health record (EHR) technology 10 years ago, a decision that "catalyzed our use of data," says Garrido. Now, the organization leverages its 10 petabytes of EHR data—and its four thousand data analysts—to push risk claims down and close gaps in care, including non-adherence. One program, called the Outpatient Medication Safety Net, uses an "adherence ratio" to predict when a patient will run out of medicine. This information—and whether a script was filled on time—is then passed to the physician through the patient's EHR. "Then the physician can say, 'I notice that you didn't pick up your statin. Let's talk about that, and why it's important and why I prescribed it, and what [barrier] might be getting in the way,'" says Garrido. "We're presenting that information to physicians to enable a conversation that in fact does increase adherence rates."



Avoidable costs of more than $200 billion are incurred each year in the US healthcare system, with non-adherence accounting for the largest share.

Transparency trigger

Of the 9.3 million patients covered by Kaiser, almost half—4.4 million, says Garrido—are active users who log in to their personal health records to view lab results, refill prescriptions, or otherwise participate in their own treatment and care. A pilot program in the northwest is going one step further by giving patients access to their doctor's progress notes from past appointments within the EHR.

The "progress notes" pilot program at Kaiser is modeled on the OpenNotes research project spearheaded by Tom Delbanco, professor of general medicine and primary care at Harvard and Jan Walker, a member of the research faculty at Harvard and Beth Israel Deaconess.

In an October 2012 *Annals of Internal Medicine* article, Delbanco, Walker and colleagues published research (funded by The Robert Wood Johnson Foundation and other charitable organizations) suggesting that physician notes, taken during an appointment, can have a substantial impact on behavior and adherence when the notes are freely shared with patients (see sidebar on page 47). The authors conclude "open notes seem worthy of widespread adoption," since "patients accessed visit notes frequently, [and] a large majority reported clinically relevant benefits and minimal concerns, and virtually all patients wanted the practice to continue." Sixty to 78% of participating patients reported an increased adherence to their medications. On the physician side, "doctors experience[ed] no more than a modest effect on their work lives," the authors wrote.

Kaiser's EHR provider is Epic, and Garrido says it's not so easy to customize functionality in the EHR, and corresponding personal health record. But Kaiser figured out a way. "We've created these smart phrases that essentially copy the physician's progress note into what is called the "after visit summary" in Epic, says Garrido. In addition to printed information given after a visit—current meds discussed, patient instructions, other physician comments, etc.—that information is also archived within the patient's personal health record and accessible at any time. The ability to refer back to exactly what a physician said,

days or weeks after an appointment, is a simple but effective tool in driving healthy behavior, Garrido says.

Plus, the notes appear in the health record without any additional typing or effort from physicians; adding another data entry requirement to a patient visit is a sure way to kill any new program, notes Garrido. Patients in the Kaiser EHR system still have to log in through a rigorous authentication system for access—which can be a barrier for some patients—but Garrido is hopeful that Epic will be able to create a button or some easy way for patients to simply mark or click for speedy access to progress notes from recent visits with physicians.

Asked about biometric data as a potential component of a patient's health record, Garrido emphasized the importance of patient reported outcomes, and the integration of a patient's perspective and experience into any treatment plan. Are patients willing to open up their biometric sensor data to health insurers? "Some patients want to do it, but it's really up to the physicians to decide why they want this data," says Garrido. "We're relying on clinicians, currently, to encourage sharing of [biometric] data."

On the flip side, not every doctor is comfortable sharing his dispassionate assessment and clinical notes with patients; it challenges the traditional notion of physician/patient hegemony by creating a medium for a patient's critique of a physician's choices. But most of the time, it probably just leads to healthy dialogue. Delbanco's OpenNotes research provides data suggesting that many apprehensions about sharing information fade with actual experience.

Rulon says Pfizer is looking at "testing out Blue Button"—a digital tool used in some CMS health plans that lets patients easily download their EHRs and other personal health data —"in clinical trials, so patients could actually access the information from their clinical trial participation…which would become part of their personal health record." The benefit, says Rulon, is that patients could more easily "see whether that medication is something that works for them, or not."

Pharmacy factor

Plenty of research has been done to prove that high adherence rates improve health outcomes and reduce costs to the system, and pharmacies understand that better adherence also means higher quarterly returns. The largest chain pharmacies have all rolled out digital services for patients (e.g., e-refills) and physicians (e.g., e-prescribing), and in May, the National Association of Chain Drug Stores (NACDS) Foundation awarded three research grants totaling $1.8 million to study "the impact of pharmacist-collaboration in helping patients manage their medications and avoid readmissions following discharge from the hospital."

Hospital readmissions are expensive, and Section 3025 of the Affordable Care Act requires CMS to reduce payments and, therefore, penalize some hospitals when patients are readmitted within 30 days of a discharge; the provision went into effect in October 2012. Historically, hospitals haven't done a good job supporting patients after they're discharged—there isn't a clear financial incentive attached to counseling patients about healthy routines and medication adherence outside hospital walls. Hospitals make money when patients walk in, not out.

In an effort to fill this gap, for patients and for hospitals worried about readmission rates, Walgreens launched "WellTransitions," a program aimed at patients transitioning out of the hospital to "make sure the patient knows what they're supposed to be doing when they go home," says Kristi Rudkin, senior product development at Walgreens. Medication regimens and schedules often get changed during a hospital stay, so WellTransitions helps patients get comfortable with a new medication routine. "I think patients generally want to do what they're supposed to do, but sometimes things get in the way," says Rudkin.

Walgreens pharmacists assigned to the WellTransitions program—which requires a "small upfront fee to the hospital"—provide medication alignment and bedside prescription delivery; patient counseling and clinical follow-up with physicians; reinforcement contact with patients at nine days and 25 days after discharge; and an monthly joint outcomes report to assess the program's effectiveness in terms of cost and readmission reductions. At the 2014 American Pharmacists Association conference last April, Walgreens unveiled data showing that patients who participated in the WellTransitions program were 46% less likely to experience an unplanned hospital readmission within 30 days of discharge.

In addition to online prescription management tools like opt-in refill reminders and therapy consultations, Walgreens, like Kaiser, is analyzing its own data for targeted interventions. "Our overall technology strategy is to leverage the systems we have and build new systems that allow us to identify the patients that need an interaction with a pharmacist, or need a certain level of service to remain adherent," says Rudkin.

As an example, Rudkin says Walgreens identifies patients filling a new prescription for the first time, and passes that information to the pharmacist, to ensure the patient gets adequate instruction. "When that patient comes back for the first refill [of a new prescription], we alert our system to tell the pharmacist right on the screen whether that patient is on time to refill, or late," says Rudkin. "The pharmacist doesn't have to do any calculations, and that enables a different conversation." Anticipating non-adherent behavior, and intervening before a refill is missed, is a powerful, data-enabled service. But Rudkin says there's work to be done. "Predictive modeling is interesting in and of itself—it's a very important component—but the other side of that is, what do we do with that information,

and how do we use it?" says Rudkin. "How do we fit that into the pharmacy workflow to make sure the patients that are struggling can be helped?"

One historical problem with refilling prescriptions—and a leading cause of the periodic pharmacy haggle so many patients have experienced—has to do with prescription alignment, or being able to get every prescription filled at the same time. Rudkin says Medicare has made "huge strides" by implementing override tools to make prescription pick-up more efficient for patients. She also hopes that more insurers will embrace longer refill periods in the retail setting, like a three-month, 90-day supply, for example, which cuts down on trips to the pharmacy, and related non-adherence.

Asked for an example of how pharma might support the pharmacy experience for patients, and facilitate better adherence through Walgreens, Rudkin called pharma's device training programs "a unique service" for patients. By delivering training and instructions to the pharmacist at the time a prescription is dispensed, these programs "help ensure that the pharmacist has a consultation with the patient prior to the sale of the prescription," says Rudkin. "In some cases, the doctor's office has already covered [device training] with patients, but even some of those patients will say, 'Show me again.' Most patients starting a new medication decide in the first three months whether they're going to continue that medication or not."

Convenience is king

Everyone has a vested interest in prescription adherence; for pharma, pharmacy, providers and payers, the interest is financial. For patients, it's personal: the return on adherence is paid in the currency of health and life, which is harder to represent on a spreadsheet (Quantified Health acolytes notwithstanding). The science of adherence seems to have pivoted in recent years away from a B.F. Skinner-flavored behaviorist approach to one focused more on behavioral economics, with the emphasis placed on money as the primary mover.

It's true that out-of-pocket costs and copays do continue to prevent patients from picking up their prescriptions. In fact, some signs point to difficulties with financial assistance programs in the health exchanges. It's an important one, but cost is only one barrier. Innovative technological approaches using narrative storytelling and gameplay— such as CyberDoctor's recently released PatientPartner app—are generating impressive data. PatientPartner asks patients to live with a disease vicariously by choosing a fictional diabetic (in this case), and making health decisions for him or her through a series of prompted "scenarios," which resemble all too real-world situations. Bad choices lead to poor health outcomes in the story, which ostensibly helps to model healthy living for actual patients by hammering home the risks of non-adherence.

At the Health 2.0 conference last October, CyberDoctor revealed the results of a randomized clinical trial with 100 non-adherent diabetes patients in Pennsylvania's PinnacleHealth System. According to CyberDoctor CEO and founder Akhila Satish, using the PatientPartner app increased medication adherence by 37%—from 58% to 95 %—or the equivalent of three additional days of drug adherence per week. Patients who read through scenarios on the app for 12 minutes during the trial brought HbA1c levels down by a full percentage point – from 10.7% to 9.7%, according to data presented by the company.

The adherence problem won't be solved by a single financial incentive, mobile app, data application, educational program, or transparency initiative. Instead, stakeholder groups across the healthcare delivery system must use all of these tools and more, to "collaborate out to the patient" and move beyond the traditional borders and segments of patient care. If organizations can't work together to push adherence rates up—when so many incentives are aligned—what hope is there for success in fixing other problems where incentives are woefully misaligned, like fee-for-service? Patients are ultimately responsible for their own health, but no one wants to hang out in the pharmacy any longer than necessary. When it comes to practicing healthy behavior, convenience is king. PE

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OpenNotes: Bending the Adherence Curve

Tom Delbanco, Jan Walker, and their colleagues' original research (published in Annals of Internal Medicine) —which would become the foundation of the OpenNotes initiative—detailed findings that startled even the most skeptical brand managers. Conducted across three primary care practices at Beth Israel Deaconess Medical Center, Geisinger Health System, and Haborview Medical Center, respectively, with 105 primary care physicians and 13,564 patients participating, study data indicates that knowing what a doctor thinks about you, and is telling you to do, is a powerful tool when it comes to adherence.

According to the published report, 11,797 patients opened at least one note, and of the 5,391 patients who opened at least one note and completed a post-intervention survey, 60% to 78% reported increased medication adherence. Fifty-nine percent to 62% of patients believed that they should be able to add comments to a doctor's note. At the end of the experimental period, 99% of patients wanted open notes to continue.

Just as importantly, few doctors (0%-5%) reported longer visits as a result of open notes, and not a single participating physician elected to stop providing notes at the end of the trial period. Few patients reported being worried, confused, or offended by the notes they read, which contradicted doctors' predictions for the experiment.

Adaptive Trial Design: Prepping for Adoption

As interest grows in this productivity-enhancing tool for seamless drug development, there is a need for a better working consensus on standardized metrics that monitor progress and certify success.

Biopharmaceutical companies are targeting improvements in clinical trial design as a critical factor in pipeline portfolio success. One major driver of change is adaptive trial design, which has been shown to improve the quality and relevance of clinical data, enhancing in turn the likelihood of a faster, more predictable path to market authorization. Draft FDA guidelines on adaptive trial design, issued in 2010, have bolstered the appeal of this tool in maintaining productive relationships with the regulator.

The high visibility given to a major breast cancer trial based on adaptive design principles—known as the I-SPY 2 program—promises to continue the industry's evolution toward endorsement of the adaptive approach. The I-SPY 2 trial represents a significant re-engineering of the clinical trial design process with the aim to rapidly evaluate the potential of new drugs in the treatment of breast cancer while reducing cost, compressing time, and lowering the number of study volunteers.

The trial incorporates several innovative features, including an adaptive design that enables researchers to use data from patients early in the trial to guide decisions about which treatments, and doses of a particular treatment, might be more useful for patients who enter the trial later. It provides a scientific basis for eliminating treatments that are ineffective and for selecting treatment that show promising efficacy more quickly. One of the other key I-SPY 2 design features is the collaborative nature of the trial in that the multiple drug candidates developed by multiple companies are evaluated. New candidates are added as others either progress to Phase III based on efficacy in specific subgroups of patients, or are dropped.

Two successful drug candidate transitions were recently reported from the I-SPY 2 trial. Veliparib (an AbbVie compound) proved promising against so-called triple-negative breast cancer, an aggressive form of the disease for which there are few effective treatments; and neratinib (from Puma Biotechnology) was reported to be similarly effective against a different form of breast cancer.

The success of I-SPY 2 has triggered similar designs in other disease areas such as the Alzheimer's disease collaborative trial recently announced by the European Union's Innovative Medicines Initiative (IMI). This €53-million project will allow evaluation of several drugs at once using an innovative adaptive design in a similar way to I-SPY 2, and involve a number of biotechnology and pharmaceutical companies working together with academic centers, patient groups, and regulators.

Estimating current adoption rates

Although awareness of adaptive trial design use has grown and qualitative reports from biopharmaceutical companies indicate that adoption is increasing, little quantitative data exists to characterize industry-wide adoption of this study design approach. Recently, two independent studies have been conducted to establish and corroborate baseline measures of adoption.

The two independent studies chose a definition of adaptive trial design that is consistent with the current FDA regulatory guidance. Specifically, *adaptive trial designs are pre-planned adaptations, generated through the use of trial simulations and scenario planning, of one or more specified clinical trial design elements that are modified and adjusted while the trial is underway, based on an analysis of blinded and unblended interim data.*

The FDA cites numerous adaptations that can be planned and prospectively written into the protocol. Examples include pre-planned changes in study eligibility criteria (either for subsequent study enrollment or for a subset selection of an analytic population); randomization procedure; treatment regimens of different study groups (e.g., dose level, schedule, duration); sample sizes of the study (including early termination); concomitant treatments used; planned schedules of patient evaluations for data collection (e.g., number of intermediate time points, timing of last patient observation and duration of patient study participation); and analytic methods employed to evaluate protocol endpoints (e.g.,

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covariates of final analysis, statistical methodology, or Type I error control).

In October 2011, the Drug Information Association's (DIA) Adaptive Design Scientific Working Group (ADSWG) conducted an online survey among 11 pharmaceutical and biotechnology companies and six contract research organizations (CROs). Participating companies reported that 475 adaptive design trials had been conducted between January 2008 and September 2011, suggesting a 22% adoption rate. Two-thirds (65%) of the total adaptive clinical trials analyzed used group sequential or blinded sample size re-estimation. One-third (35%) employed other adaptive design approaches, including unblinded sample size re-estimation, added or dropped treatment arms, and changes in randomization ratios.

In October 2012, the Tufts Center for the Study of Drug Development (Tufts CSDD) conducted in-depth interviews on the status of adaptive design implementation among 12 major pharmaceutical companies. The study was funded by an unrestricted grant from Aptiv Solutions. Tufts CSDD probed current adoption rates and their impact on study budgets and durations. The results of this study were consistent with that conducted by the ADSWG. Overall, simple adaptive designs are being used on approximately one out of five (20%) late-stage Phase III clinical trials. Early terminations due to efficacy futility were the most common simple adaptive design used. Sample size re-estimation was also a commonly used adaptive design approach. In-depth interviews with sponsor companies indicated low usage rates (i.e., 10% of clinical trials) of adaptive dose finding and treatment group adaptations (e.g., dropping unsafe or ineffective doses) and extremely low usage of seamless Phase II/III studies.

While the two independent assessments indicate that between 20-22% of all active clinical trials include an adaptive trial design approach, analyses of public and commercial databases of trial activity present a very different picture.

Two separate assessments of the Department of Health and Human Services' ClinicalTrials.Gov (CT.Gov) registry of FDA-regulated clinical trials found very small numbers of adaptive trial designs listed there. Searching the term "adaptive design," the ADSWG found only 62 adaptive trial design studies listed—among the 103,213 active trials listed in CT.Gov since 2008—a 0.06% adoption rate.

Tufts CSDD conducted a search of a broader set of adaptive trial design keywords among the 103,213 active CT.Gov trials listed since 2008. Examples of keywords searched include adaptive design, Bayesian design, sample size re-estimation, and group sequential. Tufts CSDD found 119 total trials, suggesting a 0.1% adoption rate. Tufts CSDD also manually searched 37,111 active 2012 clinical trial listings in CT.Gov and found a total of 35 adaptive trial designs listed—a 0.09% adoption rate.

Tufts CSDD also conducted searches of adaptive design keywords using two commercially available subscription-based clinical trial databases—Informa Health's Citeline and Thomson Reuters' Cortellis services. An assessment of the former database yielded a 0.2% adoption rate (317 adaptive clinical trials out of 136,000 trials listed). Tufts CSDD found 134 adaptive clinical trial designs out of a total of 146,678 trials listed in the latter database, suggesting a 0.09% adoption rate.

Next steps

Given these contrasting survey results, the establishment of a robust method of monitoring the adoption of adaptive design trials use and the specific types of adaptations utilized would be invaluable in improving senior management decision-making on study design optimization practices and their impact. However, the extremely low adaptive trial adoption rates found in CT.Gov and in commercially available databases are not plausible or credible given qualitative and quantitative assessments of current adoption levels. These call into question the quality and integrity of the data on study design practices captured there.

As an immediate next step, Tufts CSDD and the ADSWG plan to meet with CT.Gov and EudraCT system administrators and with commercial database developers (e.g., Informa Health, Citeline; Thomson Reuters, Cortellis; and Springer Science and Business Media, Adis) to broadly discuss this problem; to establish consensus-based definitions of adaptive trial designs; and to develop a formal process to capture more detailed, standardized data on various adaptive design approaches that can better inform overall decision-making.

Improvements in tracking adaptive design use will benefit drug development sponsors by providing better benchmarks on design practices and stimulating study design enhancements.

There is a critical need to improve the characterization of adaptive clinical trial designs in these public and commercial databases. Doing so would assist regulators in anticipating changes in adaptive design practices and in assessing the impact of regulatory reform on study design. Improvements in tracking adaptive design use will also benefit drug development sponsors by providing better benchmarks on design practices and stimulating study design enhancements that may ultimately drive higher levels of quality and improvements in drug development success rates. PE

Social Media and the In-House Counsel

What is and what should be keeping you up at night.

Social media plays an increasingly significant role in the US healthcare system. According to a recent poll, the average American spends more than 52 hours per year on the Internet looking for health information, but only visits the doctor three times per year. While 53% of users rely on the health information hub WebMD, others rely on more general social media sites like YouTube (12%) and Facebook (10%). Only 9% of Internet users rely on pharmaceutical companies' sites for information.

In light of the growing influence of social media, pharmaceutical companies may be considering their options when it comes to such interactions. But for these organizations, entering the social media scene is not as simple as just creating a Facebook page or learning how to tweet in 140 characters or less. Rather, social media poses a regulatory and litigation maze that must be carefully navigated. Here, we provide some insight into the most pressing questions companies are, or should be, asking about social media.

1. Should my company increase its social media presence?

Most pharmaceutical companies have only a limited presence on social media sites. In fact, according to a study released by the IMS Institute for Healthcare Informatics, "among the 50 largest [pharmaceutical] companies, half still do not use social media to engage consumers or patients." And "only 10 of the top drugmakers have availed themselves of all three of the most widely used social media channels—Twitter, Facebook, and YouTube." Some companies have Facebook pages but include no product information on them, and many explicitly inform visitors to their Facebook pages that any comments mentioning products may be deleted.

Yet, pharmaceutical companies are the logical source for the most current information about a particular product. The lack of clear regulatory guidelines may be part of the reason companies have been reticent to broaden social media interactions with patients.

Companies may want to increase their social media presence for many reasons beyond marketing, not the least of which is to provide the public with clear, unified information on the company and its products. In the absence of information directly from the company on an official or authorized social media page, companies may be able to do little to counteract potential misinformation arising out of the growing amount of anecdotal information available through mainstream social media sites. This could give rise to reputational harm that companies can do little to address after the fact.

For pharmaceutical companies, entering the social media scene is not as simple as just creating a Facebook page or learning how to tweet in 140 characters or less.

2. Does my company's Facebook and other social media presence provide fair balance?

Recent FDA activity, including the agency's letters to Institut Biochimique (IBSA) and Akrimax Pharmaceuticals and to Amarc Enterprises teach us that the FDA is indeed watching what pharmaceutical companies post on social media sites and is continuing to enforce existing advertising guidelines, including fair balance. Companies have struggled with finding ways to meet those requirements on these new platforms, and FDA has provided only limited regulatory guidance thus far. While it is still very unclear what makes for best practices in this space, once can safely assume that until there is new guidance, companies will need to provide the same fair balance information about potential risks and side effects

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in every posting as they would in any other marketing context.

FDA has not yet provided any indication that the fundamental fair balance rules will change as social media changes. However, guidelines are expected this year to provide guidance on "Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices" on social media platforms "with Character Space Limitations."

3. What is out there on the Internet about off-label use of my company's products, and what should I do about it?

Despite a US Court of Appeals' ruling in the case of *United States v. Caronia* in 2012, which overturned the conviction of a sales representative for promoting off-label uses for an FDA-approved drug, there does not appear to have been a sea change in the way companies defend claims of misbranding and off-label promotion. Nor does the government appear to be backing off enforcement efforts. Indeed, FDA publicly announced that the decision would not change its enforcement in this area.

FDA's recent draft guidance on "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" continues to limit a company's ability to provide truthful information about its product beyond the four corners of the approved label. In its first foray into social media guidance, the FDA significantly inhibits the use of these opportunities to provide information to patients.

The document limits actions a company may take in responding to "requests" for off-label information about its products, including requiring any response be made only privately to the requesting person, yet provides no guidance as to what a company should do about third-party postings on various social media and interactive sites about unapproved uses of its products but which do not specifically ask for information.

4. Do I need to correct incorrect information posted about my company's products?

Current FDA guidelines do not address what obligation a company has to monitor public statements about its products and provide corrections to misinformation. The number of interactive consumer sites—from Facebook to WebMD to comments on news articles to blogs—provides a nearly infinite range of possibilities for unrelated—and unregulated—third parties to post information about a given product on the Internet. However, all guidance to date has focused on sites or postings under the "control" of a particular company, and has not imposed any obligation for manufacturers to search the entire web.

Such a limited obligation is consistent with the March 2001 draft guidance on adverse-event reporting, that provides that a company must "review any Internet sites sponsored by them" for potential adverse-event reports, but are not required to review "any Internet site it does not sponsor." Companies have been hesitant to correct or respond to these comments for fear of being viewed as having "control" over the third-party website for both FDA and liability purposes. The agency has stated that the development of guidelines for social media "are among [its] highest priorities" and has indicated its intent to provide draft guidance on "Correcting Independent-Third Party Misinformation About Prescription Drugs and Medical Devices" this year.

5. How does social media impact my company's product liability risk?

Under traditional product liability law, a manufacturer is required to provide warnings about known and knowable risks associated with the use of its products. In the case of pharmaceutical products, most states interpret that obligation as one to provide adequate information about the safe use of the product to a patient's treating physician because the doctor "is a learned intermediary between the purchaser and the manufacturer" who is in the best "position to understand the significance of the risks involved and to assess the relative advantages and disadvantages" of a particular medication. But in the age of social media, it is reasonable to ask how the increased availability of information directly by patients will affect the application of the learned intermediary doctrine.

Thus far, few states have created exceptions to the learned intermediary doctrine despite the existence of more traditional direct-to-consumer advertising. Only West Virginia has done away with the doctrine completely, and New Jersey and perhaps Texas have limited their availability in the face of consumer advertising. How will increased availability of information—and increased use of that information by patients—change courts going forward?

The second important question to be addressed is how much of the vast information available on the Internet is chargeable to a company? Product liability law requires a company to warn about known and knowable risks, and generally holds a manufacturer to the skill and knowledge of an expert in the field. Pharmaceutical manufacturers are expected to keep abreast of scientific discoveries and advances affecting their products. Manufacturers cannot avoid liability because they chose not to review relevant scientific literature and, as a result, did not provide warnings about potential harm. But manufacturers are "*not* under a duty to warn of every report of a possible risk, no matter how speculative, conjectural, or tentative."

So, how does publication anywhere on the Internet affect a company's state of knowledge under this requirement? In other words, is a posting of a an event something a company "knew or should have known" to put it on notice? The answer is probably not. PE

Challenges to the Specialty Business Model

New constraints require new solutions.

Biopharmaceutical drug discovery companies have progressively tailored their pipelines to specialty therapeutic areas and smaller patient populations, driven by several factors: better understanding of underlying disease biology leading to significant gains in efficacy; innovation in technologies; faster development and regulatory timelines in high unmet need populations; uncertainty around generic competition entering legacy markets; and significant pricing power. An analysis of new molecular entity (NME) approvals since 2000 shows that new drugs with orphan-drug designations have steadily risen; nine of the 27 approvals in 2013 were orphan drugs. Robust pipelines in specialty areas like oncology, neurology, and immunology suggest a continuation of this trend.

However, the specialty business model has lately shown signs of strain and outright constraints in continued scalability. Agents such as Gleevec, Zaltrap, and Sovaldi have been under fire from physician groups and government officials in recent months for high price points. Companies have also increased the prices of drugs already on the market in recent years (see chart on facing page), raising questions about the overall costs to the healthcare system. A careful review of the market environment yields three key challenges to the focus on specialty indications that are particularly critical for drug companies.

- Increased competition
- Finding patients who benefit
- Market access (including accessibility, pricing, and reimbursement)

Competition

As the market for specialty biopharmaceuticals has become more lucrative, companies have naturally responded by moving aggressively into these therapeutic areas. The result has been a dramatic increase in clinical development pipelines, particularly oncology. Whether viewed through the lens of new mechanisms of action (MOA) or specific indications such as multiple sclerosis or renal cell carcinoma, multiple branded agents are now available. Even the most promising emerging MOAs such as PD-1 and CDK-4/6 inhibitors have multiple entrants in the pipeline despite their newer status and compressed clinical development time frames. This has put incredible pressure on companies to move quickly, as many of these markets exhibit advantages for early entrants or even a "winner-takes-all" dynamic due to a new product's potential to significantly raise the efficacy standard.

Finding patients

Once on the market, the challenge of finding the patients who stand to benefit has also emerged, especially for drugs that target biomarker-defined subpopulations. Timely and efficient patient identification is often essential to getting the best outcomes. However, implementing best practice screening, diagnosis, and treatment paradigms is a work in progress, often with evolving goals due to rapidly progressing scientific and clinical advances.

Innovative, value-based pricing models will be critical to securing reimbursement and continued market access of high-price therapeutics.

Market access

Finally, global healthcare systems have reacted to specialty brands in different ways. In the US market, both commercial and government payers have had limited tools to manage the usage of these high-priced medications. Despite letters from Congress and negative headlines, these agents are typically managed by cost sharing with patients, through co-insurance and/or tiering for commercially insured patients and the donut hole/catastrophic coverage in Medicare. This has raised af-

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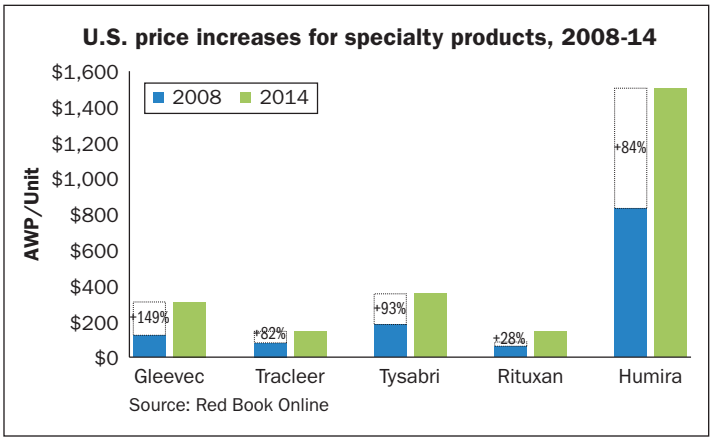
fordability issues for many patients even though they are covered by medical insurance.

Unlike the US, many European markets have restricted access to specialty drugs. In the UK, NICE has adopted a formulaic method of valuing quality-adjusted life years (QALY). Although some drugs such as Alexion's Soliris have successfully navigated this process, numerous coverage rejections have limited access and utilization of new specialty drugs.

Other free-market systems have also moved to be more restrictive. The Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany has more aggressively used comparators to new medicines, often generics, to negotiate down prices on a value basis. Further, Germany has recently debated publishing market prices post discount, a similar system to Medicare ASP pricing in the US. Many countries use Germany in reference pricing, and this would have a ripple effect of lowering drug prices across Europe and Asia.



Manufacturers have increased the prices of leading specialty drugs, such as those listed above, in recent years.

Evolution of the specialty business model

To manage these challenges, leading companies are focusing more than ever on innovation, partnership, differentiation, and value. Traditional pharmaceutical companies have been adopting new R&D models that seek to identify innovation early through new partnership structures with biotechnology companies and academic institutions alike. This focus on deal-making enables projects to be nimble with a more diverse portfolio. Further, companies are reacting to increased competition by seeking evidence of clinical and commercial differentiation much earlier in the development process to drive resourcing decisions and mitigate future risk. As clinical and commercial teams work closer together, this emphasis will result in first-in-class, best-in-class drugs that separate from current competition and existing treatment options.

Companies are also seeking to be more engaging partners once drugs are on the market. Basic market education is often needed to raise disease awareness and improve the logistical identification of patients who will benefit from a new therapy. This includes outreach to patients through advocacy groups or more directly through channels such as social media.

Close coordination with diagnostic partners and other technology providers are also often required to find patients who stand to benefit from these novel therapies. Once identified, companies are focusing on additional services such as affordability support, adherence programs, call centers, and other patient support platforms. Although adjacent to traditional drug therapy, companies that pay attention to the entire patient journey will develop their markets more effectively.

Finally, in response to global markets' focus on cost containment, leading companies are working on building health economic and outcomes research (HEOR) capabilities to demonstrate value through evidence-based medicine and comparative effectiveness. In the last 10 years, membership to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the premier HEOR society, has more than quadrupled to over 13,000 members worldwide, a testament to the growing importance of this field.

These capabilities include partnerships with academic institutions, clinicians, and managed care organizations to add credibility to these studies. Innovative, value-based pricing models will be critical to securing reimbursement and continued market access of high-price drugs. To avoid deeper discounting, new models such as risk-sharing (e.g., receiving payment only for patients who respond to therapy) may be necessary to access global markets. PE

Immune to Cancer

The Cancer Research Institute is clearing a path to the future of immunotherapeutics.

Despite a steady stream of new, highly-targeted cancer therapies entering the market in recent years, most patients struggling against the disease aren't living much longer. In terms of disease progression and death, health outcomes in oncology really haven't changed that much in 30 years.

However, the explosion of R&D efforts into immunotherapies—drugs that conspire with the human immune system to curb the haywire replication of cancer cells— represent the next best hope for patients, and for drugmakers hoping to make a splash (and a pile) in oncology.

Jill O'Donnell-Tormey, CEO and director of scientific affairs at the nonprofit Cancer Research Institute (CRI), says immunotherapies, probably in combination, will soon play a major role in the treatment of most cancers. "What has turned the tide for people outside of the hardcore cancer immunologist community is the results we're seeing in areas like non-small cell lung cancer," says O'Donnell-Tormey. "The results in melanoma have been phenomenal, but there's a feeling that melanoma is a particularly immunogenic cancer type. ... I don't think non-small cell lung cancer was ever thought of in that way."

O'Donnell-Tormey

Phase I data combining BMS's Yervoy with an anti-PD1 in melanoma brought the patient response rate up around 50 or 60%, which is promising, and the use of chimeric antigen receptors (CAR) in specific leukemia types like acute lymphoblastic leukemia (ALL) has also generated exciting early-stage data, says O'Donnell-Tormey. Novartis in-licensed a hot rod CAR candidate and "adoptive T cell" therapy from research scientist Carl June and UPenn in 2012.

Big pharma leaders in the programmed cell death (PD-1) and programmed death-ligand (PD-L1) immunotherapy space include BMS, Merck, Roche, and AstraZeneca/MedImmune. AZ fended off a Pfizer acquisition in part due to its belief that Pfizer undervalued its immunotherapy pipeline. Recent estimates by Citibank and Goldman Sachs anticipate the immunotherapy drug market to reach $35 billion and $20 billion a year, respectively, in a decade or sooner.

An important catalyst for early-stage development of new immunotherapy products, especially combinations, is the CRI's Clinical Accelerator program. Shifting from its historical focus on cancer vaccines, the Accelerator program is able to combine unapproved pipeline products—from multiple drug companies—for clinical testing. New combinations are put into clinical trials by CRI with the support of venture funds and philanthropic dollars. CRI partner, the Ludwig Institute, acts as trial sponsor. CRI gets contractual access to experimental candidates, and the owners keep their IP. "The big thing here is that these are not company-sponsored trials," says O'Donnell-Tormey.

The CRI and its clinical trial network come up with an idea and design for a trial, combining whichever drugs it sees fit, regardless of who owns the IP. "We can do some of these combinations before the two companies have to negotiate anything together. ... We're in a neutral space," O'Donnell-Tormey says.

CRI Accelerator trial results are shared, and if two companies decide to develop a combination product further, CRI is eligible for milestones. O'Donnell-Tormey describes the Accelerator as a de-risking option for companies who may not otherwise be able to test combination therapies across organizations with no upfront cost. If the trials fail, no company dollars are lost. The CRI Accelerator's biggest ongoing study at the moment is a combination of AZ/MedImmune's anti-PD-L1 drug MEDI4736 and tremelimumab, the latter (intriguingly, given the acquisition scare) out-licensed from Pfizer to MedImmune in 2011. (AZ completed its acquisition of MedImmune last October.)

June marks the second annual Cancer Immunotherapy Month, as declared by the Cancer Research Institute, and O'Donnel-Tormey says it's terrific to see the CRI's belief and mission validated, after 60 years of dedication to the field. But despite the enormous potential of emerging science and new immunotherapies in cancer, she worries about the research community. "It's a desperate time for scientists," says O'Donnel-Tormey. "NIH is cutting back, and even really senior scientists are saying they can't get grants. I think it will effect young people going into science as well—if there isn't support for them, as much as they love it and are talented in it, if you can't make a career or get your lab funded, it's a problem for science." PE

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