

POINT OF VIEW

BEYOND THE SHADOW OF A DROUGHT

THE NEED FOR A NEW MINDSET IN PHARMA R&D

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It's well accepted that pharmaceutical R&D productivity has fallen, with new drug approvals trending downward even as costs trend up. Companies are taking some actions: rationalizing costs, increasing outsourcing, collaborating with academic institutions, increasing their focus on specific disease areas, reconfiguring their organizations. But is that enough?

We don't think so. And neither, apparently, does Wall Street. Investors remain wary of R&D spending, rewarding companies that cut and penalizing those that don't—a sign of limited confidence in the industry's use of its capital. Admittedly, it is difficult to press the panic button when pharma companies' net income sits at 20 to 30 percent and the industry has sustained six percent annual growth over the past five years despite a pronounced global economic downturn. But in our view, positive earnings and scattered signs of change mask more fundamental problems.

In this paper, we will explore those problems. We will start with an attempt to put a number on just how far R&D productivity has fallen. (The answer, a shocking one, we think, is *more than 70 percent*.) We will identify the changes both in the industry and in the wider field of healthcare that have contributed to the R&D drop— and make it unlikely that the industry will return to the “normal” of five or ten years ago. We will show how the current industry mindset for drug development has become mismatched with the realities of the marketplace, and we will portray a new mindset

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that we believe must stand behind any serious attempt to make pharma companies creative, productive, and profitable in a rapidly evolving new era.

We aren't bearish on pharma. All industries go through cycles; there is no reason why pharma shouldn't, and no reason that successful companies won't emerge. If this is a reassuring thought, let us also be sobering: Whether your company is among the successful depends on how much you are willing to move the R&D organization away from historical mindsets. Companies that move forward need to be suspicious of familiar processes (have they changed enough?) and familiar metrics (do they provide enough guidance for a changed era?). The new mindset must give rise to new behaviors, and those behaviors must become an integral part of process, culture, and reward systems.

IT'S WORSE THAN WE THOUGHT

To shed light on the R&D productivity problem, we evaluated the 450 new drugs¹ approved by the FDA between 1996 and 2010. Within this cohort, we looked at three things:

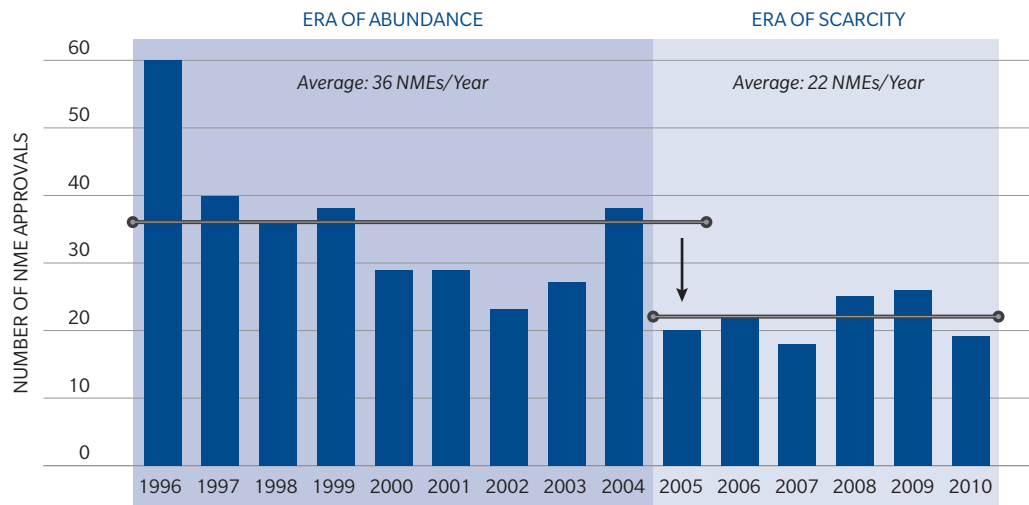
1. The number of new drugs approved by the FDA each year
2. The value of the new drugs launched each year. We used a common industry benchmark—the revenue generated by the original NME plus any line extensions in the fifth year after launch. Revenues were adjusted to 2010 dollars to enable fair comparison over time
3. The total amount invested in R&D each year, again in 2010 dollars

The 15-year study period fell into two segments: an “Era of Abundance” (1996-2004) characterized by robust approvals and high return on capital, and an “Era of Scarcity” (2005-2010) characterized by fewer approvals, weaker sales, and low return on capital. The two periods are roughly demarcated by the Vioxx withdrawal of late 2004. On the surface, this is not surprising: The withdrawal was widely seen as signaling a secular change in the fortunes of drug innovators. But the magnitude of that change is far more dramatic than we had anticipated:

Drug approvals fell by 40 percent. In the Era of Abundance, the FDA approved an average of 36 NMEs a year. In the Era of Scarcity, the number dropped to 22 (Exhibit 1). Higher scrutiny from drug regulators probably accounted for some of the slowdown in the early years. But by the end of the decade, overall industry output—despite a dramatic scale-up in R&D—reset at a lower level. Although 2011 will be a strong year for approvals (*see sidebar: “2011 is shaping up to be a better year”*), investors don't believe that a single good year signals that the R&D decline has been solved, and neither do we.

¹ Throughout the paper we use “new drug” to refer to a “new molecular entity,” or NME, whether approved under a New Drug Application (NDA) or Biologic License Application (BLA).

EXHIBIT 1: TWO ERAS OF R&D PRODUCTIVITY



Source: Drugs@FDA database

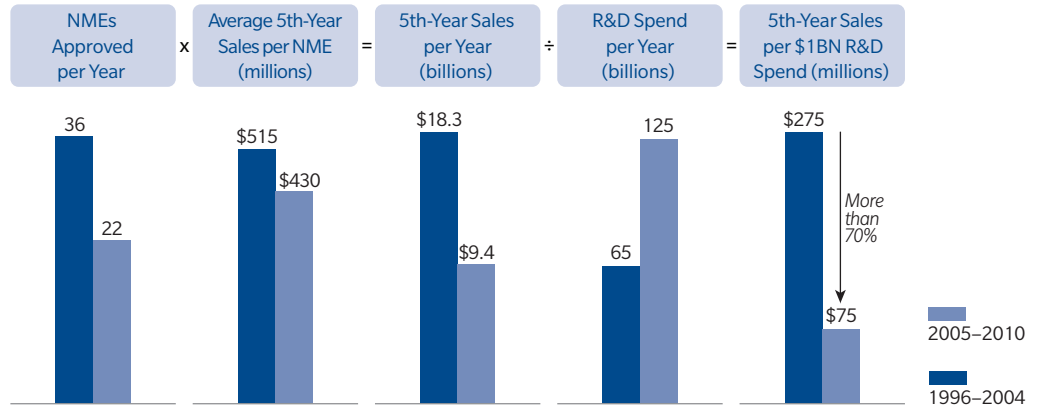
Each new drug generated less value. The average fifth-year sales for an individual drug (in constant 2010 dollars) fell from \$515 million in the Era of Abundance to \$430 million in the Era of Scarcity, a decline of more than 15 percent—and one that is all the more noteworthy because it comes after a decade when revenues realized by new launches steadily increased, driven by the globalization of the industry, a receptive pricing environment, and increasingly sophisticated sales techniques.

Moreover, the combined impact of fewer new drugs and smaller average sales translated into a 50 percent drop in value—from \$18.3 billion generated by the average new drug cohort in the first period, to \$9.4 billion during the second. This significant decrease is driven at least in part by the decline in the number of blockbusters: 12 per year in the Era of Abundance, six in the Era of Scarcity. The drop in blockbusters, in turn, is partly the result of an industry shift from large primary care categories to specialty markets. The hope had been that a larger number of “smaller” drugs would maintain overall industry momentum; our analysis shows that this hasn’t happened. The contribution from small drugs *has* increased, but only by an almost-negligible \$500 million.

R&D spending is up and productivity has declined dramatically. Industry R&D spending (even accounting for recent reductions) has skyrocketed, doubling from an average of \$65 billion per year in the Era of Abundance to \$125 billion during the Era of Scarcity. To compare productivity across eras and to calculate the value generated for every dollar spent on R&D, we combined our three fundamental measures—the number of approvals, the sales generated by each cohort, and the annual R&D investment.

By this measure, R&D productivity declined by more than 70 percent between the two periods (Exhibit 2). In the Era of Abundance, drug companies produced an average of \$275 million in fifth-year sales for every \$1 billion they spent on R&D. During the Era of Scarcity, the equivalent figure was \$75 million. The change is dramatic—fewer, less valuable drugs that cost a lot more—and it points to a deeper concern: The economics of spending \$1 billion on R&D and generating \$75 million in fifth-year sales are not sustainable.

EXHIBIT 2: INDUSTRY R&D PRODUCTIVITY HAS DROPPED MORE THAN 70%



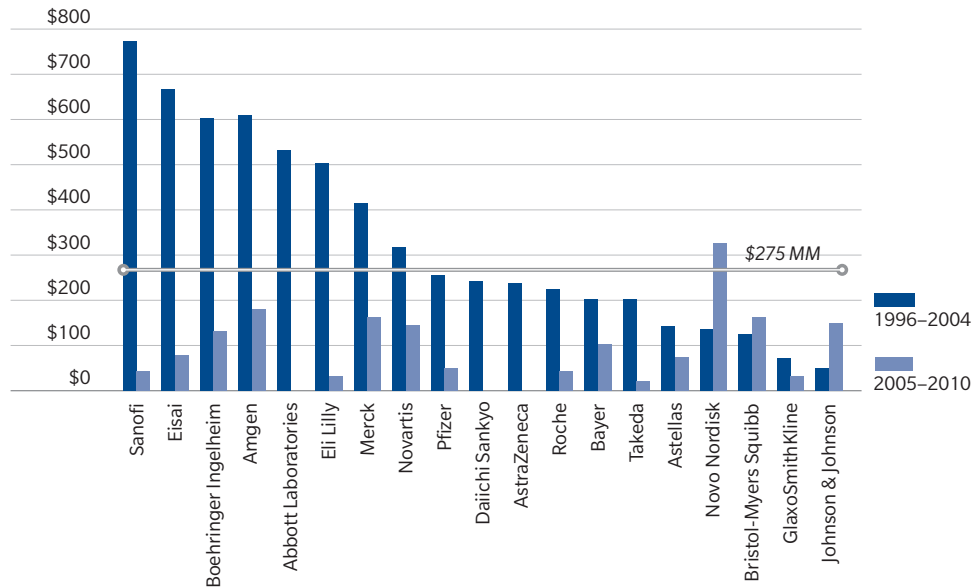
Sources: Drugs@FDA database, EvaluatePharma, Oliver Wyman Analysis

No company has escaped the secular decline. We were curious to see if any company had systematically outperformed industry averages, so we evaluated the same metrics for the 20 largest companies² across the industry. While there might not be enough data points from any one company to draw strong conclusions, and while we did observe company-to-company variance in performance, it is safe to say that the decline in productivity is secular. Seventeen of the 20 companies experienced a decline in productivity in the Era of Scarcity (Exhibit 3). No company successful during the Era of Abundance maintained high levels of productivity, and only Novo Nordisk has achieved anything close to the value leaders generated a decade ago.

The breadth of the decline is important. This is an industry that is endlessly benchmarked, where there is a relentless sharing of “best practice,” and where laggards look to the leaders to chart the way. But in R&D, no company has broken away from the pack. That tells us that we need to be more aggressive and to question the fundamental approaches to pharma R&D for solutions to the productivity challenge.

² As Teva’s revenue is largely driven by generics, they are not included in Exhibit 3.

EXHIBIT 3: FIFTH-YEAR SALES GENERATED PER \$1 BILLION SPENT ON R&D



Sources: Drugs@FDA database, EvaluatePharma, Oliver Wyman Analysis

SO WHAT WENT WRONG?

For most of its recent history, the drug industry has benefited from positive tailwinds: abundant innovation, relative pricing freedom, and a supportive political and regulatory environment. Most of the companies that grew up in this period built themselves to a blueprint for success under these conditions. Companies scaled up an industrial approach to R&D, using combinatorial chemistry and high-throughput screening against well-characterized disease targets to produce an ever-expanding stream of new products. To capture the commercial potential, the scale up in R&D was mirrored in the promotional model: Huge sales forces blanketed doctors with messages about new drugs. Because most therapies were new, there were few quality generics. Payers weren't as focused on drug spend, and cost considerations were less of a factor; annual price increases in the U.S. were frequently in the high single digits.

Today everything has changed.

In today's environment, physicians and payers alike see less value in drugs with incremental benefits.

The standard of care in many disease categories is high and rising. To some extent, pharma companies are victims of their own success. After decades of abundant discovery, many disease categories are well supplied with safe and effective therapies—once-daily pills that control symptoms or modify disease progression. And many are cheap: in the U.S. overall penetration by generic drugs reached 78 percent of prescription volume last year, up from 63 percent in 2006.³ In a separate study,⁴ we evaluated the changing nature of opportunity across 127 diseases, scoring each on the level of innovation taking place, the priority that payers gave it as a driver of cost, and the remaining headroom—the unmet need that could still be addressed by new drug therapies. Strikingly, in 62 of 127 diseases, representing 57 percent of global pharma sales, headroom for new drugs was limited.⁵ This is especially troublesome in today's environment, in which physicians and payers alike see less value in drugs with incremental benefits. A recent example: Eli Lilly's antiplatelet therapy Effient launched with a nominally superior profile to Plavix (the gold standard). In the past, it could have expected to capture substantial market share. But not today. In 2010 Effient notched sales of only \$115 million, or just two percent of the sales for Plavix.

Payers have found their voice, and they are using it. Rapidly rising healthcare costs are now a political and economic challenge in every mature economy. Payers are scrutinizing every category of expenditure, including drug spend, and they have become increasingly aggressive about using their purchasing power to push back on prices. For example, last year the largest U.S. insurer, UnitedHealthcare, pitted two competing insulin therapies against each other to address rapidly rising costs in diabetes treatment. The two leading insulin suppliers, Novo Nordisk with Novalog and Lilly with Humalog, faced off in a direct competition on price, with the winner gaining sole Tier 1 status for their therapy.⁶ Humalog won, and in states where UnitedHealthcare

2011 IS SHAPING UP TO BE A BETTER YEAR

In a relatively rare case of good news, 2011 has been a very strong year of approvals. As of this writing, 25 new drugs have been approved by the FDA. More importantly, six of them are projected to be blockbusters: Xarelto (blood clot prevention), Incivek (hepatitis C), Brilinta (platelet inhibitor), Victrelis (hepatitis C), Benlysta (lupus), and Yervoy (melanoma). Many of the products approved this year offer significant improvements in the standard of care; for example, Benlysta is the first lupus drug approved in 56 years. Does this mean that the industry is back on pace to achieve the throughput and growth it enjoyed in the late 1990s and early 2000s? Unfortunately not. We evaluated the 180 NMEs projected to launch between 2012 and 2014 and found that when the expected output of these three years is combined with the strong 2011, the level of projected 5th year sales approved remains at the "Era of Scarcity" level of \$9 billion.

³ Source: IMS Health

⁴ Oliver Wyman analysis, 2011

⁵ The study defines therapeutic headroom as room for improvement in efficacy, safety, or route of administration.

⁶ Most other insurance companies regard Novalog and Humalog as equivalent and place both on Tier 2. UnitedHealthcare sought to provide a lower cost alternative for their patients and placed Humalog on Tier 1.

Persistent high attrition suggests that the way we are studying drugs is not working, and needs to change.

has a strong presence, new prescriptions of Humalog have increased 22 percent, while new prescriptions of Novalog have increased only one percent.

Government payers are asserting themselves as well. In 2010, the German government took direct aim at pharmaceutical pricing in the AMNOG law, which requires companies to prove additional benefit over existing therapies with a “value dossier” submitted at the time of marketing. Without proof of additional benefit that takes into account the cost of therapy, new products will be subject to fixed pricing. Already some innovative companies are choosing to “sit out” of the German market, as Lilly and Boehringer-Ingelheim did in September 2011, when they announced that in light of AMNOG they were cancelling the German launch of Trajenta.⁷ Sitting out one market may be an option, but if constraints like these spread, pharmaceutical companies will have to adopt different tactics relative to payers.

Rising payer power is having knock-on effects. It used to be that pharma could drive sales even for “me too” products by upping the call-volume of its powerful selling machine. This tactic has become significantly less effective. Doctors are increasingly bound to treatment pathways and formulary restrictions, while pharma companies face more and more constraints on what they can do or say with doctors.⁸ The industry’s collective sales force in the U.S. has shrunk from 100,000 to 75,000 over the last five years,⁹ and the downsizing may not be over yet: 70 percent¹⁰ of physicians say they see fewer sales reps than they used to, and 23 percent¹¹ report not seeing any.

Finding new drugs is tougher than before. The science being pursued in pharma R&D today is simply more challenging. Recent advances in the understanding of disease biology have led us to realize that many of pharma’s highest-priority targets—degenerative conditions such as Alzheimer’s disease or rheumatoid arthritis—are more diagnostic classifications covering multiple conditions than focused diseases with a common symptom profile and disease etiology. In cancer, activity is shifting to higher mortality tumor settings, including pancreatic, brain, and esophageal cancer. These are settings in which the organ must survive both surgery and drug therapy (unlike breast, prostate, and colorectal cancer) in order for the patient to survive. Tough stuff indeed.

While some would debate whether the science has gotten harder, there is evidence that attrition has increased. Oliver Wyman analysis shows that the likelihood that a new drug entering Phase III will reach the market is just 50 percent, far less than the success benchmarks many companies commonly use. Another study shows that success in Phase II has fallen from 28 percent to 18 percent in recent years.¹² The problem is not only that higher attrition leads to fewer drugs; persistent high attrition suggests that the way we are studying drugs is not working, and needs to change.

7 According to Bloomberg, the companies said “the mechanisms Germany plans to use in its cost-benefit analysis will lead to an inadequate consideration of the therapeutic benefits and positive properties of the drug.”

8 A year after Minnesota limited gifts by pharma companies, primary care physicians in Minnesota were twice as likely to decline visits from sales reps as the national average. (Source: *The New York Times*).

9 Source: *The Wall Street Journal*, May 10, 2011.

10 Source: Sermo.

11 Source: Physician Profiling Firm SK&A, August 15, 2011.

12 Source: Thompson Reuters.

The dozen largest pharma companies have declared a “focus” in oncology, neurology, and diabetes; 10 have a focus on immunology.

Some attribute increased attrition at least in part to greater regulatory scrutiny, and there are indeed signs that the FDA has taken a stricter stance, particularly with regard to safety, in the years since the Vioxx withdrawal: Pre-Vioxx, the FDA issued between 20 and 35 black box warnings each year; in the years after, that figure rose to between 60 and 80. In testimony before Congress in July 2011, Jonathan Leff of Warburg Pincus gave voice to concerns about the FDA: “While many factors have contributed to the escalating cost, time, and risk of new drug development, a changing regulatory environment at the FDA is the most significant.”

It is not the intent of this paper to shed light on the FDA’s motivations; but we do want to make two important observations: 1) With respect to safety, higher scrutiny is not likely to go away; and 2) it is the inevitable result of an increased standard of care. Where there are already safe, cheap, and effective drugs (for instance in osteoarthritis, acid control, and asthma), the burden will be on the industry to demonstrate that new innovations convey an appropriate ratio between *incremental* benefit and risk. Again, pharma finds itself trapped by its earlier success.

Pharma capabilities aren’t fungible; cancer and diabetes are fundamentally different.

Pharma companies used to enjoy huge success in managing for serendipity: They emphasized shots on goal, and when they got a hit in research, they put more or less fungible development resources behind it. If a drug made it to market, they built a field force around it, or leveraged the existing primary care machine. Pretty much every large pharma company played in the same dozen or so therapy areas, and competitive differentiation focused on power in sales and marketing—the “Glaxo,” “Merck,” and “Pfizer” models all had their day.

But the changes reshaping the industry—cheaper generics, more aggressive payers, and denser, tougher, rarer science—have upped the competitive requirements. Now even very large companies are realizing that they can’t compete effectively in every therapeutic category. Just about every CEO has announced a major refocusing of the R&D footprint and a reduction in the number of research focus areas from a broad set to a few. More attention is being paid to specialization of capabilities and integration of focus areas from research through to commercialization.

While these are positive developments, we worry that few large pharma companies have really differentiated their strategies: The dozen largest pharma companies have declared a “focus” in oncology, neurology, and diabetes; 10 have a focus on immunology. All have reduced emphasis on primary care, reduced their field forces, and announced a commitment to specialty products. This begs several questions: Is this really the best use of global R&D expenditure? Can all 12 companies (or even five or six) credibly claim leadership in each of these areas? Has anyone really *achieved* a new degree of focus?

Looking across these changes, the bottom line is that many of the fundamentals for the industry have shifted to the negative—tailwinds have become stiff headwinds. There are many pockets of experimentation and some success, but the dramatically changed environment merits a significantly stronger response than the industry is providing today.

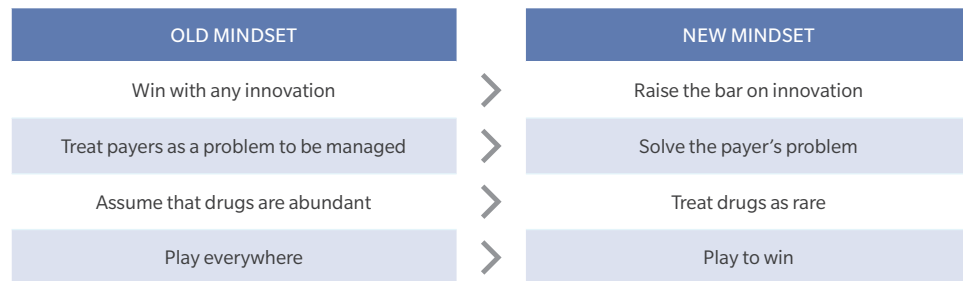
HOW PHARMA COMPANIES NEED TO CHANGE

What would a fresh approach look like? To a certain extent the answer is simple: create more and better products, while spending less. But for that to happen, companies will need to make four primary shifts in their mindset:

- Raise the bar on product innovation
- Do more to solve the payer’s problem
- Treat drugs not as predictable or abundant, but as rare
- Make concrete moves toward differentiation and focus

These are not controversial statements. Similar imperatives can be heard in the strategy pronouncements of many pharma companies. But when we look beyond words, at what pharma companies *do*, we do not see enough evidence of the change needed to reverse the productivity problem.

EXHIBIT 4: THE SHIFT IN MINDSET



Source: Oliver Wyman Analysis

» RAISE THE BAR ON INNOVATION

With an established standard of care in more than half of all drug categories and greater sensitivity on cost, physicians and payers have less patience for new drugs that don’t make therapy significantly more effective or less expensive. The disappointing sales of several recent launches—including Effient, Fanapt, and Onglyza—were in part due to the lack of a strong value proposition compared to existing therapy. We see several ways for pharma to raise the bar, and bring meaningful improvements to even crowded drug markets.

Payers are likely to accept comparatively high prices for drugs that significantly improve the standard of care for a clearly identified set of target patients.

Focus on the core of efficacy. With doctors balking at novel drugs that don't move the needle over generics, the goal in development has to be finding and targeting patients for whom the drug has the greatest benefit. This reverses the classic approach, which targeted the broadest population in which the drug had a statistically significant (if marginal) result. Biomarkers and patient stratification are important clinical tools, but they must be used to bolster the value proposition to the healthcare system. For example, Pfizer's recently approved lung cancer therapy, crizotinib, targets the five percent of lung cancer patients with the ALK oncogene, but it has demonstrated very high efficacy—reducing tumor size in 57 percent of patients and stopping disease progression in 87 percent. Crizotinib is expected to generate revenues of more than \$500 million by 2015, despite targeting just 50,000 patients globally. Payers, public and private alike, are likely to accept comparatively high prices for drugs that significantly improve the standard of care for a clearly identified set of target patients.

Invest up-front to expand options. In a funding-constrained environment, companies face pressure to outsource, shorten, and focus early clinical studies—but this may just shift risk downstream and increase late-stage attrition. With novel mechanisms and broadly potent drugs targeting many diseases, the cheap-and-fast approach is probably inappropriate. In most cases, companies need to spend more to fully understand where and for whom their drugs work. Pfizer ran parallel, early stage studies in five diseases with their JAK inhibitor, tofacitinib, and their broad approach has put them in an advantaged position.

Increased safety and ease of use can be innovative—think “Easy Button.” When Merck launched Januvia in type two diabetes, some commentators criticized its relatively small effect on HbA1c. But these critics were ignoring the drug's strong safety profile and ease of administration, as well as the substantial investments Merck had made to position Januvia at the heart of second-line therapy for type 2 diabetics. Januvia itself is easy to take—a once-daily pill with minimal side effects. The Janumet combo (of Januvia and metformin) was ready within months of the Januvia launch. Merck did a lot to show doctors and patients that even with a relatively small effect on blood sugar, Januvia could give patients positive reinforcement in addressing their disease.

One has to wonder what was in the minds of developers of the other 17 DPP-IV inhibitors in clinical trials when Januvia launched. Were they thinking as broadly as Merck about the value proposition? How did the companies beyond third or fourth position plan to add value to the treatment paradigm? Did others further back believe our health system could need five or six—let alone 18—DPP-IVs?

Cooperative efforts to improve the effects of drugs by improving adherence would benefit pharma, health outcomes, and, in many cases, overall costs.

» SOLVE THE PAYER'S PROBLEM

Simply put, pharma has to stop treating payers like the enemy in pricing and rebating strategy and get on the same side of the table in helping them manage cost. In a system straining to “bend trend” or “slow growth” in healthcare cost, annual high-single-digit price increases on branded therapies are as welcome as a kick in the shin. In our view, successful pharma players will take a different approach and will treat payers as customers.

Understand payers' challenges. With rapidly aging populations in the mature markets and rising standards of care in the emerging markets, payers are under pressure globally to slow the rate of healthcare cost increases. In the U.S., the Affordable Care Act (ACA) and the changes it is accelerating will put enormous pressures on payer margins, as health plans are forced to include more low- or negative-margin consumers in state exchanges or Medicaid programs. If ACA is implemented as written, Oliver Wyman expects that typical payer margins will decrease by at least 35 percent—and potentially more than 50 percent. More broadly, ACA has set in motion a set of changes in healthcare that will make payers and providers more accountable for the health value of all therapy. Accountable care delivery models, population-based reimbursement, and health IT-enabled transparency will drive the shift from a fee-for-service model—which has undeniably served pharma well—to fee-for-value. The central objective of this shift is reducing the overall cost of treating a patient, while improving quality of care.

Where is pharma in the midst of these tectonic shifts? Many novel therapies have the potential to make a real difference in the balance of cost and outcomes of treatment. Cooperative efforts to improve the effects of drugs by improving adherence would benefit pharma, health outcomes, and, in many cases, overall costs. But by and large, pharma is sitting out this transformation. Rather than embracing opportunities to engage in risk sharing with novel therapies or population based pricing, pharma is too often using rebates to undermine formulary strategy and pushing material annual price increases.

Actively seek opportunities to enable the payer's success. Historically, relationships between pharma companies and payers have skewed toward antagonism. Some push and pull between the two sides may be unavoidable. But pharmaceutical companies need to shift beyond simply thinking of payers as customers and think of them as partners. Consider the relationship between P&G and Wal-Mart, two corporate giants whose relationship is mutually beneficial, but also laden with conflict around pricing, competition with store brands, etc. P&G has established a dedicated Wal-Mart team, based essentially next door to Wal-Mart's corporate headquarters. This team works closely with Wal-Mart on a daily basis to advance both companies' missions—

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cooperation in the face of conflict has proven to be a winning strategy. Pharmaceutical companies need to seek out similar opportunities to partner with key payer customers on areas of common ground, particularly in enabling providers to improve care delivery in high-cost conditions. The partnership can take many forms: above-brand programs aimed at improving diagnosis, patient stratification, continuity of care, and medication adherence; patient education; design of new provider metrics that ensure appropriate focus on quality; rigorous health data analytics; and others. Helping payers get increased value from medicines through better, smarter use is in everyone's best interest.

Conduct trials that demonstrate real-world value to payers. The pharma industry spends billions annually on pharmaco-economic and health outcome studies, producing results that payers find at best unhelpful and at worst highly suspect. Clinical trials are still primarily designed to demonstrate efficacy in the broadest population, rather than identify the patients who will receive the greatest benefit from the drug. Comparators are often carefully selected to maximize demonstrated benefit, and as a result it is no surprise that health economic results are difficult to translate into real-world clinical practice.

What if pharma companies took a different tack, and proactively studied endpoints of critical value to payers? Imagine an approach in which the Economic Proof of Concept—a clear assessment of a drug's impact on total treatment cost—was developed in parallel to the traditional measures of safety and efficacy? Some are already taking steps in this direction. Sanofi and Medco are collaborating in the design of clinical trials—leveraging Medco's knowledge of pharmacy spend—that will demonstrate value over comparative products in a manner more useful to payers. Similarly, AstraZeneca has teamed up with WellPoint to leverage their database of 44 million covered lives and determine the most effective and economical treatments for diseases, both to optimize the use of existing drugs and to guide the design of future therapies.

Leading companies recognize that the landscape has shifted and that health value proposition will be an important factor in determining product success. They actively consider risk and value to payers when setting a new drug's development strategy. Embracing the health value perspective might entail more time, cost, or risk, but there is value in a stronger pricing dossier or speedier access. And if you don't proactively study the health value proposition of a new drug, chances are your competitors will. For example, Novartis recently published a study¹³ that showed that preventive treatment with Amgen's XGEVA costs \$300,000 per avoided pathologic fracture, vastly more than its own oncology therapy Zometa. Competition on the basis of health value is well underway.

¹³ Wu EQ, et al "Number needed to treat and treatment cost per fracture avoided with denosumab compared with zoledronic acid in patients with breast cancer with bone metastases" *MBCS 2011*; Abstract 151.

As R&D leaders shift their perspective regarding the rarity of drugs, they need to increase their strategic focus on the quality of R&D.

» TREAT DRUGS AS RARE

There is abundant evidence—from Oliver Wyman and many others—that pharmaceutical R&D does not scale. Drugs have always been rare, and they have become only more so, at least for the time being. While few dispute this, old heuristics still apply: “Drug R&D is an industrial process to be optimized.” “Put more money in, and drugs will arrive reliably and with tolerable volatility.” “Speed to market dominates other considerations.”

The industry’s recent experience in the area of lipid therapy exemplified this challenge. Five years ago several companies—Pfizer, Merck, and Roche amongst others—were pursuing CETP inhibitors, an important new class of HDL-raising therapies. Pfizer, with torcetrapib, was in the lead, and by combining the new agent with Lipitor, they had the opportunity to create an efficacy fortress and extend the significant value of their lipid therapy franchise. But speed was of the essence if the combo was to launch before Lipitor lost exclusivity. Despite having seen signals of increased hypertension in Phase II studies, Pfizer chose to move forward with a landmark 25,000-patient Phase III trial. Unfortunately, the trial showed conclusively that torcetrapib increased cardiovascular events rather than reducing them. In contrast to Pfizer, Merck chose to slow development of its CETP inhibitor, anacetrapib, to investigate the hypertension signal. They proceeded only after they found that it appeared to be a torcetrapib-specific effect, and was not class-wide. In results shared at the 2010 AHA, Merck showed that anacetrapib raises HDL by 138 percent, without the side effects of the Pfizer molecule. What is this worth? Analysts currently project that anacetrapib will achieve peak sales ranging from \$3 billion to \$5 billion.

In many respects, Pfizer did everything right. They assessed a known risk and took a bold move in the face of considerable upside. They invested close to a billion dollars on a program that would have positioned torcetrapib powerfully at the time of its launch. But with the benefit of hindsight, we see different approaches that Pfizer could have taken. Rather than emphasizing speed, could they have slowed the program to better understand the hypertension signal? Rather than massing investment against a single shot, could they have accelerated back-up molecules to determine if they had a different safety profile? More radically, could they have used their leading position to strike a partnership with Merck or Roche to share the investment and risk across CETP inhibitors, and decrease the chance that they might miss out on a major therapy breakthrough in a chosen focus area?

Options like these—slowing down to learn and iterate, advancing multiple interrelated bets in parallel, leveraging the “crown jewels” in partnerships—were rarely considered in the Era of Abundance. As R&D leaders shift their perspective regarding the rarity of drugs, they need to increase their strategic focus on the *quality* of R&D, particularly as it relates to the traditional priority placed on the efficiency of R&D investment. To accomplish this shift, there need to be changes to the culture of decision making.

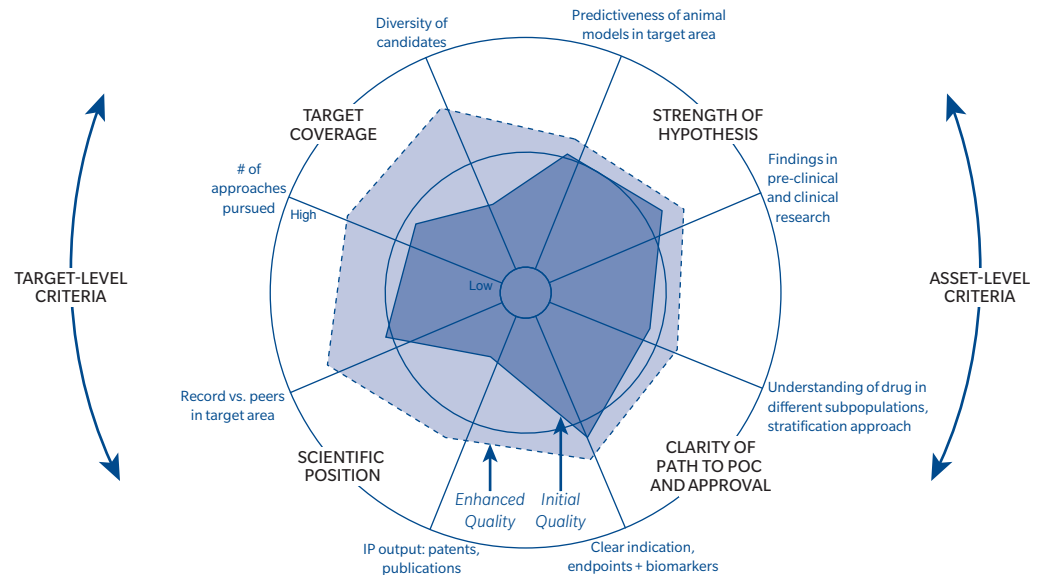
Don't overemphasize speed to market. For years, R&D leaders have taken it as dogma that “every day of delay costs a million dollars.” Order of entry remains important. But as development has become harder, there is often much “research” to perform even after human trials begin. In this environment, overemphasizing speed leads to throwing good money after bad. Sometimes, in the face of surprising clinical results, it is better to slow things down to get perspective on a molecule, and either back up and pursue other options or alter the approach going forward. Lilly's CHORUS program, which resequences development activities to enable a less expensive proof of concept, enables more molecules to be explored, while accepting a potentially slower time to market for winners.

Focus, rather than spread, investments. Pharma's current portfolio management approaches are particularly good at optimization—prioritizing the investments available in a company's portfolio. But they underplay issues of R&D quality—where are we best positioned scientifically to succeed? They are indifferent to the potential value of a drug target: as long as the investment to access a small target is scaled appropriately, it can be just as attractive as dollars spent against a target of greater value. With drug flow down and innovation hurdles up, we think this is wrongheaded. Companies can't afford to miss out on a major breakthrough in their focus areas. They need to focus investment on their most strategically important targets—those that represent the greatest pool of value, and in which they have the strongest scientific position.

Know when you might be wrong and hedge your bets. In categories where there is a partial standard of care and which involve more novel and esoteric mechanisms, companies have to acknowledge that research produces imperfect knowledge. Animal models are often poor predictors of human safety and efficacy. Problematic signals often appear only after a drug has seen exposure in very large populations. To find the right drug for a given target, several variants of a mechanism might have to advance well into human trials. If multiple variants aren't available in-house, it may make sense to seek them externally via partnerships or licensing. This can't be done for every drug target, but for the most valuable, spreading bets will maximize learning and increase the confidence in large late-stage investments.

Learn from your competitors. For any one company, and at any given time, more than 90 percent of the research activity in the industry is taking place someplace else. Some of it is likely better. An important step in improving R&D quality is to aggressively benchmark internal activity vs. the competition: How effectively are you covering the most valuable drug targets in your chosen areas? Are you satisfied with the density and the diversity of your program against a target in light of what you know about other routes being explored? Are you confident that the approaches you have selected are better than those of your peers? Are you advancing one or two molecules because you think they are the best, or because you can't afford to do more? How can you hold options on multiple approaches, to minimize your chances of missing out on an important new advance?

EXHIBIT 5: ADDRESSING R&D QUALITY



Source: Oliver Wyman Analysis

At a time when new drugs are scarce, it will be hard—but absolutely necessary—to put R&D quality ahead of traditional measures of productivity. Companies need to begin by defining a framework to measure and differentiate the fundamental quality of their R&D. Exhibit 5 represents Oliver Wyman’s approach to do just that. It is meant to complement rather than replace existing quality frameworks, and differs from others in two important ways: 1) It starts with an outside-in view of quality—explicitly comparing the science being pursued within a company to that of industry peers; and 2) it raises the unit of analysis above the individual trial or molecule, to address the density of coverage pursued against high-value targets. The framework can be used both to understand quality in a portfolio and to identify strategies for improving it.

» PLAY TO WIN

How would an advocate of competitive leadership view the strategies articulated by leading pharma companies? In our view, he or she would be hard pressed to tell them apart. Most players have announced that they are moving into specialty markets—specifically, oncology, neurosciences, immunology, and diabetes. Virtually all intend to increase external collaboration, and source more of their portfolios from licensing or partnerships. Lately there has been a shift toward “optimizing” (that is, cutting) R&D spend in order to invest more in emerging markets, specifically China. Superficially, it’s hard to differentiate across companies, or surmise who is building areas of true competitive advantage.

With high standards of care, more challenging science, and greater complexity in payer and provider relationships, category shifting isn't so easy anymore.

It was less important to build deep strength in focus areas during the Era of Abundance, because the economics of the industry were able to support single-drug franchises. Get a hit in the clinic, and you could build a business around it, redeploying medical and marketing resources from one blockbuster category to the next. But with high standards of care, more challenging science, and greater complexity in payer and provider relationships, category shifting isn't so easy anymore. There is fierce competition to establish relationships with scientific and medical leaders who have an impact on everything from trial enrollment to formulary position. Key stakeholders are harder to access and influence. It is challenging and expensive to develop a differentiated position, but it is critical companies do so.

There is ample evidence of the advantages of focus. At various times, BMS (in oncology) and Pfizer (in cardiovascular medicine) achieved influence and respect which conferred real advantages in R&D and marketing. More recently, Roche (Genentech) in oncology, and especially monoclonal antibody therapy, has achieved a degree of distinction that provides advantaged access to scientific collaborators and licensing deals, plus power to shape physician practices. A recent Oliver Wyman study on focus showed that category leaders completed 2.2 times more deals, had 5.5 times the revenue, and had 70 percent higher success rates in development compared to firms without critical mass in the disease area.

So what do companies need to do to achieve meaningful advantage? We see four imperatives:

Elevate strategy beyond individual assets. Decision-making frameworks that focus on the incremental value of individual assets sometimes ignore the advantages that come with deep history or breadth in a particular disease area. Sometimes the whole is greater than the sum of the parts. In which categories does your track record give you greater confidence scientifically and commercially? Where do you have the agility to spot problems early on and adjust course if needed? How can you leverage strength in an area across multiple molecules, or from one generation of therapy to the next?

Rigorously assess capabilities of the competition. A pharma company can't be confident in the quality of its R&D unless it knows what others are doing. How do you stack up against your peers in terms of patents and publications? Who is pursuing similar or different science in your chosen areas of focus (and are you confident that you are on the right track)? How do objective outsiders rate your research and development prowess compared to your competitors? Would you trade positions (or portfolios) with a competitor if you could?

For the highest-value and most difficult targets, we see opportunities for companies to pool R&D efforts, much as the oil and gas industry has done when pursuing high-risk, high-cost investments.

Make business development everyone's job. In part to advance the objective of knowing the competition, business development needs to be an integral part of the R&D process, rather than a gap filler when times get tough. Leaders in a category will maintain a network of collaborators to assure a steady flow of scientific insight and intellectual property. If internal efforts in a focus area slow down or encounter challenges, there should be a ready set of alternate approaches—internal and external—that can be accelerated to maintain competitive position. Business development should also be an honest broker of internal position versus the competition, providing an early signal when the company is falling behind and needs to trade or partner, rather than blindly pursue internally sourced assets.

Leverage alternative financing and consortia to access more science. Equity markets currently favor cutbacks in pharma R&D spending, but companies that hope to achieve category leadership in the Era of Scarcity will likely need to *increase* their aggregate investment. In a constrained capital environment, companies need to think creatively about program financing to increase the density and diversity of investment in high-value targets. One interesting model is Lilly's CHORUS program, which leverages externally sourced molecules from venture groups to expand the company's access to new science. For the highest-value and most difficult targets, we see opportunities for companies to pool R&D efforts, much as the oil and gas industry has done when pursuing high-risk, high-cost investments in deep water, Central Asia, and West Africa. Such consortia have conferred multiple advantages on participants: decreasing the cost and risk of high-value projects, accessing the best global knowledge and capabilities, and reducing the chance that an important industry breakthrough will be missed.

As we look across these four transformations, it is important to acknowledge the important role of culture and reward systems. When they are not aligned with the desired change or transformation, they can create substantial stress in organizations. Leaders need to alter the stories they tell. They need to redirect the focus of spontaneous notice and recognition. They need to stop celebrating speed and tolerating off-strategy, low-value activities and start talking about people who make tough choices to slow down or go outside to get R&D right. Incentives need to give less weight to milestone accomplishments and more to measures of quality and strategic intensity. The challenge is that the necessary shifts in culture and rewards take us away from metrics that are easily captured and heuristics rooted in historic patterns of success. Measures of quality and strategic intensity are significantly more nuanced and in some cases, at odds with precedents.

Companies should realize that their current metrics are likely helpful but insufficient.

HOW SHOULD PHARMACEUTICAL COMPANIES IMPLEMENT THESE CHANGES?

When setting R&D strategy, successful companies will make a robust assessment of competitiveness in their chosen disease areas. They must ask themselves, “Where can I focus that will leverage my current advantages?” and “How do I know how strong we are compared to others?” The less specific the answer, the more pressing the need to abandon an outdated or vague notion of focus. Gaps in capability should suggest alternatives to build advantage—independently, via consortia, or through other creative means—or exit.

Portfolio decisions need a similarly fresh and frank reconsideration. Companies should realize that their current metrics are likely helpful but insufficient. Risk-adjusted return—the “productivity index”—was effective when investment choices were independent and additive. Today, as individual investments become more interconnected and volatility increases, companies need metrics focused on quality, metrics that shed light on the broader market for science: How do our assets and capabilities compare to the competition’s? What is the breadth and density of approaches we are pursuing? How do these investments link to our strategy for specific disease targets?

Individual product development strategies will change. The key questions are not, “How fast can I get to launch?” or “How do I tap into the broadest patient population?” but, “What’s the highest value I can achieve?” and “What path gives me the greatest confidence?” This includes changes in how we ensure that clinical objectives represent meaningful improvements, how we match our science to patient markets large and small, how we de-risk development programs in an increasingly high-risk endeavor, and how we compete in a commercial marketplace that will increasingly look to value.

In designing individual trials, the goal should be sharp decision-making that leads to robust trade-offs that are smart about using resources and offer better risk-adjusted returns. It is no longer acceptable to gold-plate every trial in the name of “covering all the bases.” Having unnecessary information along the way may build comfort, but it won’t enhance value. Sometimes it is better to conduct a smaller trial and raise the hurdle for success. A guiding consideration should be the *value of information* that is obtained with each component of trial design. Is the insight to be delivered valuable relative to its cost? Will it have a material impact on the predictive power of the study? Will it reduce the risk of the trial or increase options downstream?

Ultimately, not all of the players in the industry will take these actions and not all will be successful. Getting the R&D organization on a path for success requires significant leadership and carefully executed change efforts. Some organizations will dismiss the need to do more, pointing to the set of initiatives already under way. We believe that those who think differently and take more significant action will be tomorrow's leaders. The first step is an objective assessment of the current mindset behind drug development decision making. This will uncover significant opportunities to improve. Then it is up to leaders to pose new questions, leverage new metrics, and take action in the parts of the portfolio most in need of change.

ABOUT OLIVER WYMAN

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