



Escaping the sword of Damocles:
Toward a new future for
pharmaceutical R&D

Recent years have seen a collapse in the industry's R&D productivity and a loss of faith in its innovation model. Regaining customers' and shareholders' trust by delivering life-changing new drugs is still an achievable goal, but it will require discipline, creativity, and luck in equal measure.

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Damocles was a courtier in Greece in the fourth century BC. The story has it that he used to flatter the king by saying what a marvelous life he had. When the king offered to swap places with him for a day, Damocles agreed, only to find himself sitting beneath a huge sword that was hanging by a single hair from a horse's tail. He couldn't move without putting his life in danger. The episode taught Damocles a sharp lesson about the gravity of a leader's responsibilities.

The trends of the past few years can be likened to a sword of Damocles hanging over the pharmaceutical industry. Yet there are good reasons for continuing to believe in it. Unmet needs, scientific advances, and increasing affluence should translate into continuing opportunities to innovate for the benefit of patients. We expect to see evolution at the core and revolutions at the periphery, as well as some fundamentally new R&D ideas.

So what does this mean in practical terms? As we discuss below, companies must adopt a different approach to their R&D spend, create more exciting environments to attract the brightest scientists, find ways of creating an ownership mindset, and embrace collaboration and co-invention to take R&D beyond the walls of their organization.

A decade of doubt

The pharmaceutical and biotech industry has failed to meet shareholder expectations over the past decade, and has come nowhere near beating the R&D odds. Indeed, R&D looks like a rigged game. Though a few companies have bucked the trend, the jury is still out on whether they are making genuine improvements to their models that will stand the test of time.

In the past 25 years the industry has created in excess of \$1 trillion of shareholder value, but destroyed around \$550 billion of value during the "decade of doubt" from 2000 to 2010. That value destruction coincided with a 60 percent increase in the R&D spending rate from 10 to 16 percent of sales, and with an even higher increase in absolute spend as worldwide sales grew from \$200 billion in 1995 to \$800 billion in 2009.

A recent McKinsey analysis calculates that the average economic return on R&D has dropped from between 13 and 15 percent in the 1990s to between 4 and 9 percent in the past decade (Exhibit 1). This suggests that much of the current investment in R&D is not creating value. We estimate that cumulative success rates have fallen by as much as 50 percent as the number of drug development programs and the cost per program have doubled.¹ For the

companies under the most pressure, the net present value of their pipeline is negative.

Not surprisingly, stakeholders and shareholders are losing patience and exerting mounting pressure on boards, CEOs, and executive teams to acknowledge the situation and reduce R&D costs. In addition, it is widely believed that one-off launches may show only ephemeral improvements in return on investment and encourage bravado, hiding deeper issues about growing trial costs, falling success rates in virtually all therapeutic areas (TAs) and molecule types, more crowded markets, higher bars for commercial success, and the unexpectedly swift loss of the partnering advantage.

As yet there is no evidence that the trend has bottomed out and success rates are improving. Things may get worse before they get better, a view endorsed by most serious industry observers.

Admittedly, some companies have beaten the odds, but whether their success is down to sustainable value creation or serendipity is unclear. Many pharmaceutical companies have had significant 25-year shareholder value creation, although their results for the past ten years are more modest (Exhibit 2). These success stories don't point to one promising direction that the industry can follow; rather, several fields have pockets of excellence that seem to pay off. Tempting though it is to wonder

Exhibit 1: Economic return on R&D investment for top 10 biopharma players

Includes impact of working capital, property, plant, and equipment, and goodwill

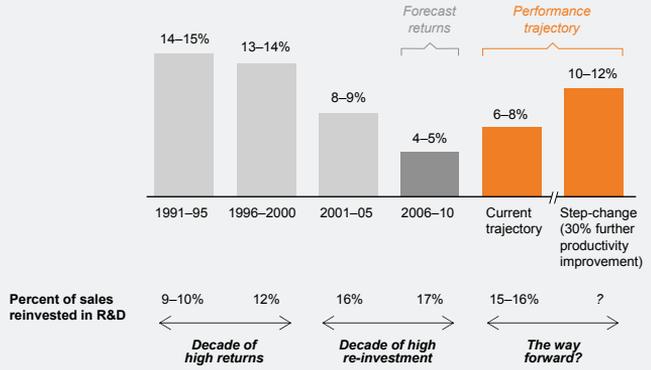
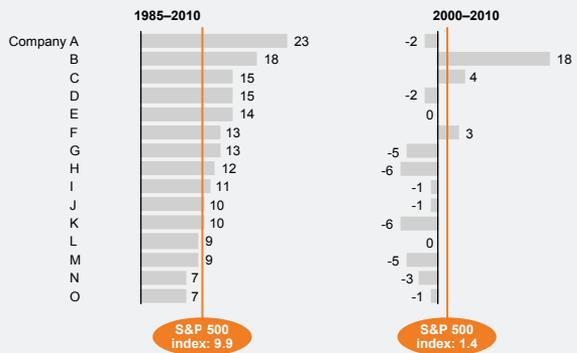


Exhibit 2: Players are losing their ability to outperform the market

Selection of top 20 pharma and biotech players
Total return to shareholders, CAGR, percent



whether TA specialization is a winning model, or whether the future might lie in higher exposure to biologics, for every such trend there are counter-examples and reasons to suppose that the opposite conclusion might be equally valid.

The environment is getting tougher

Those who take a pessimistic view can point to still more headwinds that will hold back R&D productivity.

Most low-hanging fruit has already been picked. Libraries have been screened and monoclonal antibody approaches have been run on all obvious extra-cellular targets. Expensive technology investments in such areas as functional genomics have not yet paid off, and it is unclear whether they ever will. The industry is suffering from a surfeit of similarity, as evident in the massive competition in oncology and elsewhere among many players circling a handful of targets. No one has really cracked how to capture advantage from the emerging science around disease biology and understanding, biomarkers, and model-based drug development.

Regulatory environments remain challenging in the post-Vioxx world. New medicines are unlikely to be approved without major risk management measures or label restrictions. The progress made by regulatory science in adapting to new model-based drug development approaches has been limited. Recent favorable reviews of applications appear to reflect good science rather than a change in processes, productivity, or risk tolerance.

Remnants of the old “shots on goal” paradigm persist in the portfolio. High attrition in Phase II and III may continue for several more years if lower-quality compounds continue to be pushed forward instead of getting weeded out.

A major new post-approval hurdle has emerged. Pricing, reimbursement, and health technology assessments are

getting tougher on drug profiles, and the US is no longer immune. As real-world outcomes become more and more important, there is limited willingness to pay for efficacy alone. Countries with formal cost-effectiveness assessments in drug-funding decisions now account for some 60 percent of global prescription sales, a number that is growing fast. As a result, most companies’ internal innovation hurdle has shifted beyond “me too” strategies toward earlier screening (as early as lead optimization) for differentiation against the evolving standard of care. As payors grow ever more sophisticated and more and more technologies and techniques for personalized or “protocolized” healthcare become available, the differentiation requirements for individual drugs will become increasingly specific.

Returns for many companies will deteriorate further. That isn’t because there are no advances left to make, but because too many duplicative bets are being placed by relatively low-skilled resources that are the legacy of excess investment during the artificially high profit umbrella of the late 1990s. Put simply, this is a case of overcapacity—and the capacity with the lowest productivity will be removed from the market. This is already happening through the R&D restructurings, mergers and acquisitions, and site closures seen throughout the industry in the past couple of years.

Not all doom and gloom

For the optimists among us, however, there are bright spots that provide some hope.

Investigational new drug (IND) filings have come down by 17 percent in the past few years. This is a clear sign that

excess and unproductive capacity is starting to be removed (Exhibit 3).

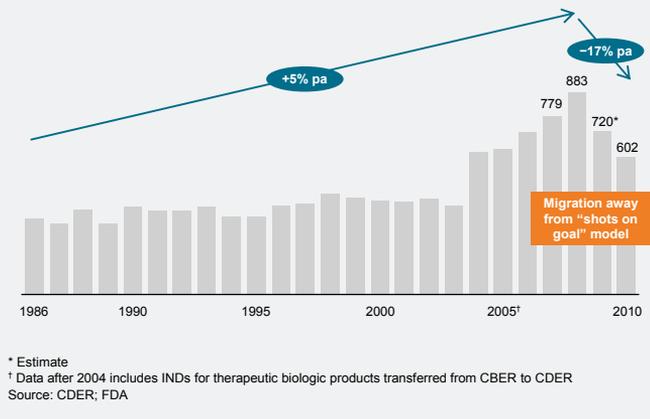
Numerous players are piloting new ideas successfully. Examples include Novartis's pathway approach; multiple companies' proof-of-concept strategies; heavyweight teams and streamlined decision-making processes; GlaxoSmithKline's modularization into ever-smaller performance units; Lilly's Chorus; numerous Covance-like contract research organization (CRO) deals; and many partnerships.

The industry's understanding of biology is expected to improve over the next decade. Entrants with new talents, skills, and orthogonal perspectives are joining the party: the NIH, the FDA, academia, the Bill & Melinda Gates Foundation, and many governments. Fresh opportunities may emerge in modeling and simulations, biomarker identification and usage, and the use of outcome data as a way to focus and guide clinical trials. The potential opportunity, and big cost, of massive bioinformatic and genomics, proteomics, and metabolomics tools and insights could finally start to pay off.

These advances could eventually open the door to the world of personalized healthcare. This would present major uncertainties for the industry's business model, but clear opportunities for better treatment of individual patients—and hence commercial potential. Better biology, better and less costly genomics, and personalized medicine may also allow some failed molecules of the past to be resurrected.

Exhibit 3: IND filings decline

Number of commercial investigational new drugs

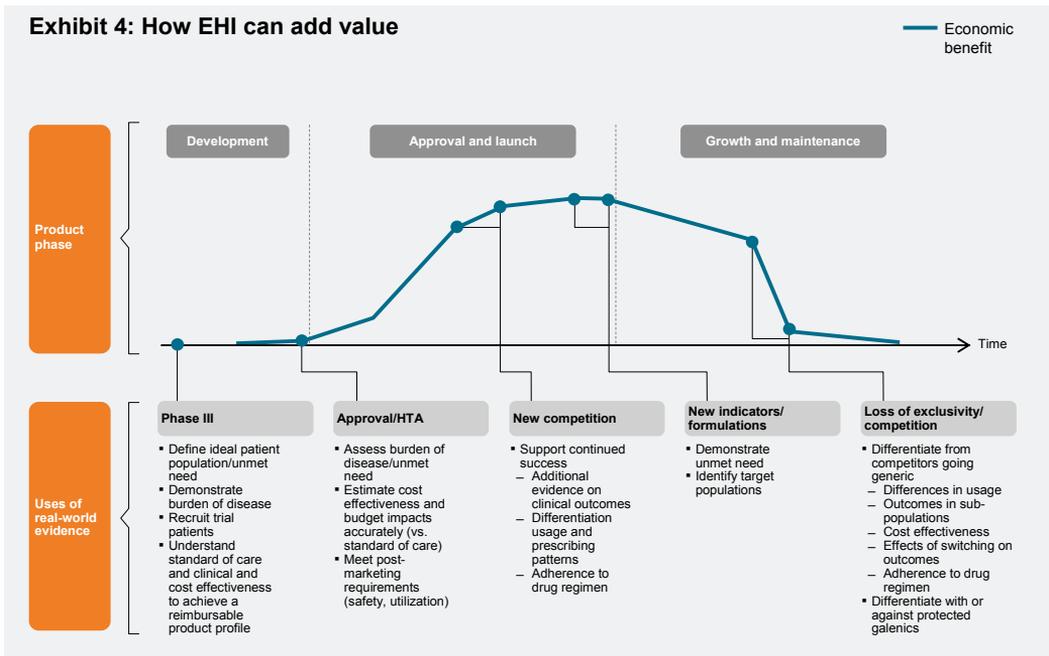


Regulators are starting to recognize that regulatory science must improve. They are also beginning to understand that a new type of dialogue with industry is needed.

Electronic health information (EHI), e-trials, and real-world evidence could create significant value across the product lifecycle. For example, they could inform trial design and decision making and improve market access by providing more robust data on comparative effectiveness and safety (Exhibit 4).

Evolution at the core, revolutions on the periphery

The R&D strategy and operating model we see for the future is one forged around variabilized—and in most but not all cases reduced—spend. We also see evolutionary but deep changes at the core, complemented by targeted revolutionary bets in a few game-changing areas. This will require an overall reduction in the number of programs, a Darwinian discipline in portfolio development and



decision making so that only the strongest programs survive, and an ownership mindset among R&D leaders and project teams so that resources are used much more thoughtfully, “as if we owned the assets and the company ourselves.”

We expect companies to focus on well-known levers to make the smaller number of programs more effective. Reorganizations and mergers will be much less important than, for example, quality of governance, senior team decision-making processes, metrics, incentives, and a culture of innovation. We also expect to see some creativity and willingness to experiment.

Our view of what will drive superior R&D productivity is based on lessons from the past as well as the pressures and opportunities we have outlined. Some of our predictions are well supported and consistent with industry views; others are more speculative and controversial.

“Variabilize” and possibly reduce R&D investment

The days of the “shots on goal” model are numbered.

There are not enough quality pipeline assets and validated targets in discovery or the clinic to launch so many shots while maintaining a formulaic investment of 15 to 20 percent of sales. Instead, we expect companies to take “quality” shots on goal starting from new libraries and sources of targets. Standard high-throughput screening (HTS) approaches and numbers-based incentives will be supplemented or even abandoned.

It’s time to make the level of R&D spending more flexible.

R&D outlay need not be fixed at 15 percent of revenue, nor at the 1990s level of 10 percent. Instead, companies could flex it between 5 and 25 percent depending on portfolio quality, pipeline evolution, and fluctuations in the quality of external assets. They could pursue opportunities that show genuine promise and be ready

to reduce or increase funding as each case dictates. Before they can do this, though, companies will have to dismantle fixed infrastructure—a process that has already started across the industry.

Redundant capacity must go. Obvious overlaps are already being removed through partnerships in R&D, such as that between Boehringer Ingelheim and Eli Lilly in diabetes. Partnerships and alliances are a natural way to reduce capacity while continuing to access good science in the therapeutic areas that are strategically valuable.

Teams should act as owners, not managers, of R&D assets. The concept of “better owner” has been poorly applied to R&D assets. It requires a mindset that an R&D team doesn’t consider itself distinctive unless it genuinely is, and leaders who are prepared to make dispassionate decisions to sell or licence out compounds that may be more valuable in others’ hands. For example, it is not clear that many companies can be distinctive in more than five therapeutic areas and multiple disease biology areas unless they have huge budgets and scale. Better ownership also requires leaders who view investments as if they were their own, and companies that enable and empower them to do so. Companies should create incentives to kill programs when necessary, and make it clear they do not regard a program kill as a career-limiting move.

Pursue evolutionary but deep changes at the core

R&D will not be transformed overnight, nor will there be a paradigm shift. The priority should be purposeful execution against well-known but often poorly executed levers:

Enhance the environment you offer.

Make your R&D organization the Apple or Google for ambitious scientists. Attracting, developing, and ensuring collaboration among the brightest researchers and “drug hunters” truly matters.² Place as much emphasis on creating a stimulating environment as on driving efficiency.

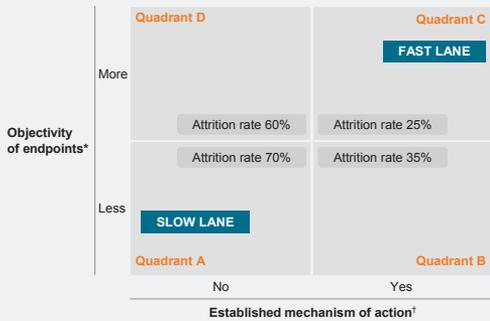
Ensure clear differentiation in a challenging payor environment. This is about medical and clinical and cost-effective differentiation, not just novelty. Creating cross-functional alignment on what differentiation means and allocating funds appropriately are key. So is conducting evidence-based drug development in real-world settings.

Make the most of your differentiated assets. Improve the effectiveness of your lifecycle management (LCM) as a way to add value to a franchise. The scarcest and hence most valuable of all assets is an approved molecule. It is important to create a franchise that can expand the brand, perhaps even beyond the active pharmaceutical ingredient, while maintaining the brand equity.

Take a Darwinian approach to decision making. Evaluating the portfolio objectively, eliminating decision-making biases, and allowing only the best programs to survive are critical. We find it’s almost impossible for a management team of non-scientists to act as responsible stewards of a research portfolio; conversely, scientific teams often find it difficult to be dispassionate. Companies seldom get a truly independent read on their pipeline quality, but when they do, it can yield valuable insights. Possible approaches to achieve this include creating a “blue-ribbon FDA” that applies the same level of scrutiny to a draft dossier as the FDA would, bringing the same

Exhibit 5: Segmenting the portfolio into “swim streams”

Based on estimates of approximate aggregate attrition rates for medicines in the following therapeutic areas: central nervous system, endocrine, cardiovascular, infectious diseases, oncology, and respiratory



* More objective endpoints relate to more easily reproducible diagnostic tests or measures, as opposed to less reproducible scales or patients' self-reporting diaries
 † Novelty of mechanism is more relevant than objectivity of endpoints
 Source: Evaluate; Pharmaprojects; Factiva; McKinsey analysis

Devise a new incentive model.

Basing incentives and goals only on the number of filings or the size of a portfolio destroys more value than perhaps any other action in the industry. To rekindle a culture of innovation while simultaneously managing scientists, leaders need to create performance metrics and incentives that promote R&D quality and output rather than just throughput efficiency (which often takes care of itself when resources are constrained). Companies

cross-functional lens to evaluate internal assets as in-licensed molecules, and adopting a venture capitalist's approach to R&D decisions. Indeed, the trend toward more VC and investor funding of development programs may well be driven by the dispassionate analysis that such leaders bring to decision making rather than by the funding itself, which usually comes at a high cost of capital.

Avoid making Toyotas in a Lexus factory. Companies should consider segmenting their portfolio into “swim streams” that move at different speeds through steady waters or rapids, internally and externally (Exhibit 5). They should systematically differentiate the way they treat R&D projects not just by value, but also by risk and data clarity. This would determine how teams are staffed, how much frontloading to do, and when it is necessary to go external. Companies should also decide their strategy in terms of “which water to swim in”—the kiddie pool or the piranha-infested stream?—for each therapeutic area and for the portfolio as a whole.

should put in place a system that enables the best biologists and chemists to work in the highest-value areas and allows them to have portfolios at all levels, an excess of ideas and investment options, and limited funds. Instead of putting people in a position where they have to prosecute bad molecules to avoid ending their careers, give them incentives to suggest better avenues to pursue.

Improve basic efficiency and effectiveness.

High levels of waste and gold-plated solutions can still be found in R&D, and indeed in pharma as a whole. Staff who join from other industries are frequently surprised by the lack of discipline in cost management. Companies should adopt methods such as lean, outsourcing and offshoring, and external spend management and oversight.

Amplify your discovery and clinical research expertise.

It is extraordinarily challenging to design laboratory or clinical experiments that are both informative under all possible outcomes and tailored to regulatory and real-world success factors. Too many experiments fail because of subtle design flaws. Developing a pool

of seasoned researchers is one of the most obvious productivity levers, yet many get it wrong. Every company has a small group of world-class researchers; the best companies figure out how to amplify their contributions by helping them build the next generation of leaders in scientific and medical research.

Consider revolutions at the periphery

Potential game changers or “new paradigm” solutions include:

Next-generation licencing or drug co-invention. If pharmaceutical companies could collaborate as effectively as high-tech and movie companies do, significant value could be created. Biology research should happen less through in-house efforts and more through early-stage collaborations. Strategy should revolve around fractional bets on a larger portfolio of molecules. Opportunities exist to separate out who funds, who prosecutes, and who markets a molecule, and to craft multi-party agreements to make that happen. Another way to create a “co-invention” ecosystem is to undertake deep collaborations with academics.

A scale-up of faster, cheaper “drug to proof of concept” paradigms.

If the Chorus model proves to be feasible at scale, it could be emulated by others. Pharmaceutical companies could do what carmakers do and work with multiple partners in emerging markets to help them develop from service providers with individual slivers of the value chain to more integrated participants in the development process.

Small, empowered, entrepreneurial R&D units. Ever since GlaxoSmithKline launched its Centers of Excellence for Drug Discovery (CEDDs) concept more than 10 years ago, there has been much

discussion on the optimal size of an R&D unit. Is it 200 to 300 researchers or as few as 50 to 70? Or should even smaller units coordinate networks of increasingly global contract research organizations (CROs) to get the work done, while planning, strategy, and design are the preserve of a team of high-caliber scientists and medics? More companies are likely to experiment with such models. In time, they may even lead to the complete disaggregation of the industry value chain as CROs take over the lion’s share of operational work.

Revisiting R&D strategy

Although it would be unwise to over-generalize about R&D operating models, our “outside-in” view suggests that most companies have room to improve. They don’t have to nail every single factor that we have highlighted, but they do need a base level of performance in most of them, coupled with genuine distinctiveness in a few. Most companies would find it useful to consider the following questions:

- Instead of setting a top-down budget, such as dedicating 15 percent of investment to R&D, should we assess our pipeline and external options as candidates for investment and build a bottom-up budget to allow greater flexibility from year to year?
- What are the therapeutic and other areas where we are truly distinctive and have critical mass? Would a venture capitalist or the FDA reach the same conclusions? Should we refine the number and mix of therapeutic areas we cover?
- Could we embrace and institutionalize a mindset to address the “fourth hurdle” to development—the market access challenge—to ensure effective LCM?

- How “Darwinian” are our R&D governance and decision-making processes? Are there biases we should eliminate? Do we strike the right balance of risk for internal and external candidates?
- What could we do to improve our efficiency and effectiveness?
- How could we benefit from broader partnerships, drug “co-invention” approaches, and an environment of “borderless R&D”?
- What other revolutions could we embrace: faster “drug to proof of concept” paradigms, more entrepreneurial R&D units, government collaborations?

Companies have tried or are trying most if not all of the approaches we have described above. It isn’t yet clear what will work and what won’t. The right mix of interventions is likely to vary from one company to another, given the differences in starting points.



After a decade-long crisis in R&D productivity, there is much sound thinking on how to do things better. What’s more, many companies are improving parts of their business, and some are managing to outperform in most or all of it. The real challenge is being able to change at scale: not only individual functions and therapeutic areas, but major companies and ultimately the industry as a whole. Perhaps pharma will then be able to put its decade of doubt behind it and embrace a decade of change.

Notes

1 For more detail on the decline in success rates, see “The anatomy of attrition revisited,” pp. 24–7.

2 For more on this topic, see “Managing the health of early-stage discovery,” pp. 28–33.

Ajay Dhankhar is a director in McKinsey’s New Jersey office, **Matthias Evers** is a principal in the Hamburg office, and **Martin Møller** is a principal in the Copenhagen office. The authors wish to acknowledge the contributions of many colleagues to this article, in particular Lynn Dorsey Bleil, Sylvain Milet, Lucy Perez, Tejash Shah, Nav Singh, and Nicole Slezak.