

Evolution or revolution?

McKinsey perspectives on drug and device R&D 2012

Evolution or revolution?

McKinsey perspectives on drug and device R&D 2012

Contents

1. Introduction: Evolution or revolution?

2. 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.

[Ajay Dhankhar](#), [Matthias Evers](#), and [Martin Møller](#)

12. New frontiers in financing and collaboration

By taking advantage of a range of innovative financing and partnership models, companies can place more bets with less money, less work, and less risk. For maximum impact, they should apply these models across their whole portfolio, not on a compound-by-compound basis.

[Eric David](#), [Amit Mehta](#), [Troy Norris](#), [Navjot Singh](#), and [Tony Tramontin](#)

24. The anatomy of attrition revisited

An update of our 2010 study reveals that the steep decline in R&D success rates continues. Small-molecule pipelines have shrunk for the first time, partnered molecules are no longer stars but remain better bets than home-grown assets, and big pharma has declined faster than the industry overall.

[Matthias Evers](#), [Jennifer Ferrara](#), [Usoa Garcia-Sagues](#), [Mateusz Kus](#), [Martin Møller](#), [Jessica Ogden](#), and [Katarzyna Smietana](#)

28. Managing the health of early-stage discovery

Productivity in the laboratory can be boosted by adopting best-practice behaviors in five critical areas: talent, collaboration, problem solving, project management, and strategy. Although the behaviors are not new, few research organizations are addressing them systematically.

[Ajay Dhankhar](#), [Michael Edwards](#), [Mubasher Sheikh](#), [Daniel Simon](#), and [Tony Tramontin](#)

34. How the best labs manage talent

It's no coincidence that the highest-performing labs across industries use the best talent-management practices. What matters most is recruiting for potential, nurturing people, recognizing success, and building diversity.

[Wouter Aghina](#), [Marc de Jong](#), and [Daniel Simon](#)

40. Value-driven drug development: Unlocking the value of your pipeline

Even safe and effective drugs struggle to gain regulatory approval and market access. R&D and commercial teams should adopt a new paradigm: collaborating at the beginning of Phase II to keep a laser-sharp focus on stakeholder value.

[Matthias Evers](#), [Petra Jantzer](#), [Valentina Sartori](#), and [Michael Steinmann](#)

48. Applying pharmacometrics in drug development

The emerging science of pharmacometrics provides powerful approaches for supporting important drug development and regulatory decisions. Applying it in clinical trials provides economic and public health benefits that far outweigh the costs.

[Sandra Allerheiligen](#), [Jogarao Gobburu](#), [Mark J. Goldberger](#), [Richard Lalonde](#), [Steve Ryder](#), [Navjot Singh](#), [Brian Smith](#), and [Amy Yozviak](#)



52. Design to value in medical devices

As price pressures increase, medical device makers need to rethink their product development processes. Design to value can help get costs under control while delivering exactly what customers want.

[Sastry Chilukuri](#), [Michael Gordon](#), [Chris Musso](#), and [Sanjay Ramaswamy](#)

60. Supercharging pharmaceutical technical development

Technical development need not be a source of delay, expense, and frustration; it can be a driver of competitive advantage instead. By adopting a holistic approach rather than making piecemeal changes, companies can make big improvements in lifecycle costs and product quality.

[Doane Chilcoat](#), [Ted Fuhr](#), [Michele Holcomb](#), and [Jatan Shah](#)

68. What will it take to develop complex biosimilars?

The coming decade will usher in the second era of product development in the global biosimilar market. Scientific teams seeking to leverage global platforms will need to understand differences in regional requirements, what it will take to satisfy them, and how competitors may respond.

[Karsten Dalgaard](#), [Sanjiv Talwar](#), and [John Whang](#)

76. Breakthrough R&D for emerging markets: Critical for long-term success?

Pharma companies pursuing growth in emerging markets will increasingly need to adapt their portfolio to address local requirements. The right R&D strategy will involve reducing costs so that they can develop innovative drugs tailored to emerging market needs and still make a profit.

[Sanjiv Talwar](#), [Shail Thaker](#), and [Matthew Wilson](#)

84. R&D strategies in emerging economies: Findings from a McKinsey cross-industry survey

Two-thirds of executives from a range of industries say their companies conduct R&D in emerging markets, but less than a fifth develop products specifically for these markets. Executives also report that underdeveloped management skills and a lack of knowledge sharing remain challenging.

88. Can innovation hubs help cure the ills of pharmaceutical R&D?

Companies grappling with rising R&D costs and uncertain results are looking to source innovation externally, but that isn't their only option. By organizing around innovation hubs—and perhaps even helping to develop new ones—they can improve their access to creativity, talent, and influence.

[Chris Llewellyn](#), [Dmitry Podpolny](#), and [Tamara Rajah](#)

96. Debunking the myths about R&D talent in China

As major global pharma companies look east to build new R&D facilities, they should be wary of conventional wisdom about conditions in China. To get the most out of their investment, they will need to pay close attention to their talent development practices.

[Cornelius Chang](#), [Jay Chiang](#), [Keith Lostaglio](#), [Laura Nelson Carney](#), [Jeremy Teo](#), and [Fangning Zhang](#)

106. Closing the R&D gap in African health care

A system governed by Africans in Africa is needed to provide a sustainable funding mechanism that would encourage African scientists to collaborate on common health concerns, share expertise, and build capacity.

[Raymond De Vré](#), [Emiliano Rial Verde](#), and [Jorge Santos da Silva](#)

114. About the authors

Introduction: Evolution or revolution?



In 2010 we published *Invention reinvented*, our first collection of McKinsey perspectives on pharmaceutical R&D. Its primary theme was that continuing to create new drugs in an increasingly harsh environment will require companies to reinvent established approaches to R&D.

This remains true today. Downsizing continues, and the number of R&D programs is starting to decline for the first time in decades as a result of the restructuring, partnering, and cost-cutting activities that have become the norm for the industry. Put simply, the pharma industry is still firmly in the grip of an R&D productivity crisis that has lasted for more than a decade. Although it is always possible to find signs of improvement and reasons for optimism, investors and management teams appear to believe that things will get worse before they get better, and so they are removing R&D capacity, especially fixed capacity.

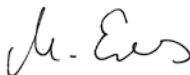
There has been much talk of a new R&D paradigm, but it is far from clear that full-scale change in one direction is the solution to the problem. Indeed, we believe that what is needed is a deep evolution at the core complemented by revolutions at the periphery, as opposed to industry-wide structural change. Some of these revolutions will inevitably turn out to be meaningful improvements that can be scaled up across companies and across the whole industry.

In this collection of articles, we explore both evolutionary and revolutionary concepts of change in drug and device R&D. The articles follow three broad themes: managing the value of pharmaceutical R&D, including thoughts on innovative ways of investing in R&D activities and securing financing; performance improvement in R&D, including perspectives on early discovery, medical devices, and technical development, as well as the latest attrition trends; and geographical aspects of R&D, with a spotlight on emerging markets and the notion of innovation hubs. Most of the articles focus on research and development for drugs, but many of the ideas also apply to devices, and one article is dedicated to this topic.

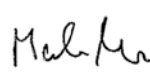
We hope you find this collection stimulating and inspiring, and we welcome your feedback. Please feel free to contact the authors directly (see “About the authors” for details), or email us at life_r&d@mckinsey.com.



Ajay Dhankhar
Director
New Jersey office



Matthias Evers
Principal
Hamburg office



Martin Møller
Principal
Copenhagen office

A close-up photograph of a sword's hilt. The guard is intricately carved with a knot-like pattern. The pommel is also knotted. The blade is visible, showing a sharp edge and a central groove. The background is a blurred map with various colors and lines.

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.

Ajay Dhankhar, Matthias Evers, and Martin Møller

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

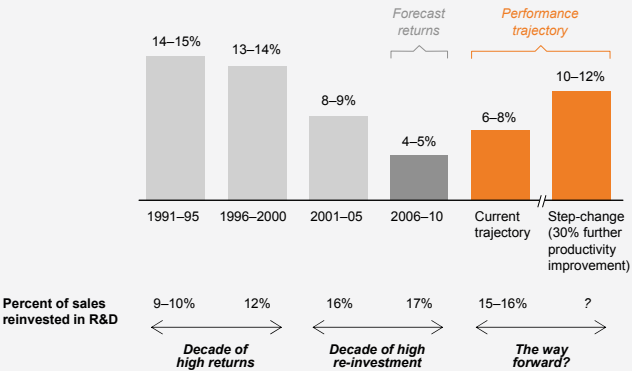
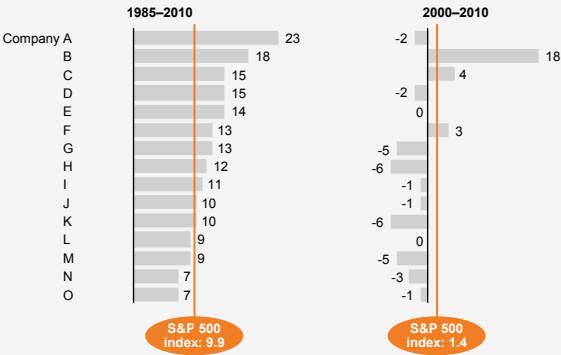


Exhibit 2: Players are losing their ability to outperform the market

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).

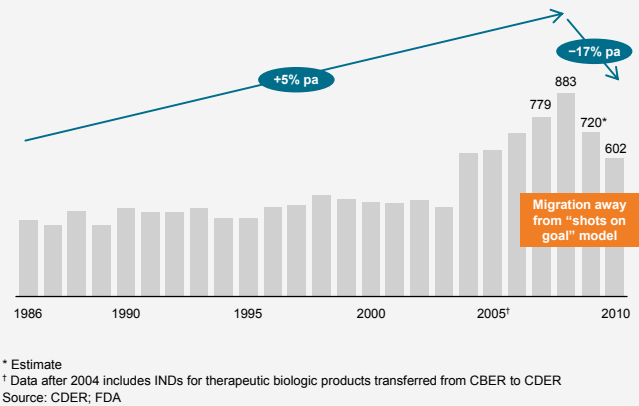
Numerous players are piloting new ideas successfully. Examples include Novartis’s pathway approach; multiple companies’ proof-of-concept strategies; heavyweight teams and streamlined decision-making processes; GlaxoSmithKline’s modularization into ever-smaller performance units; Lilly’s Chorus; numerous 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

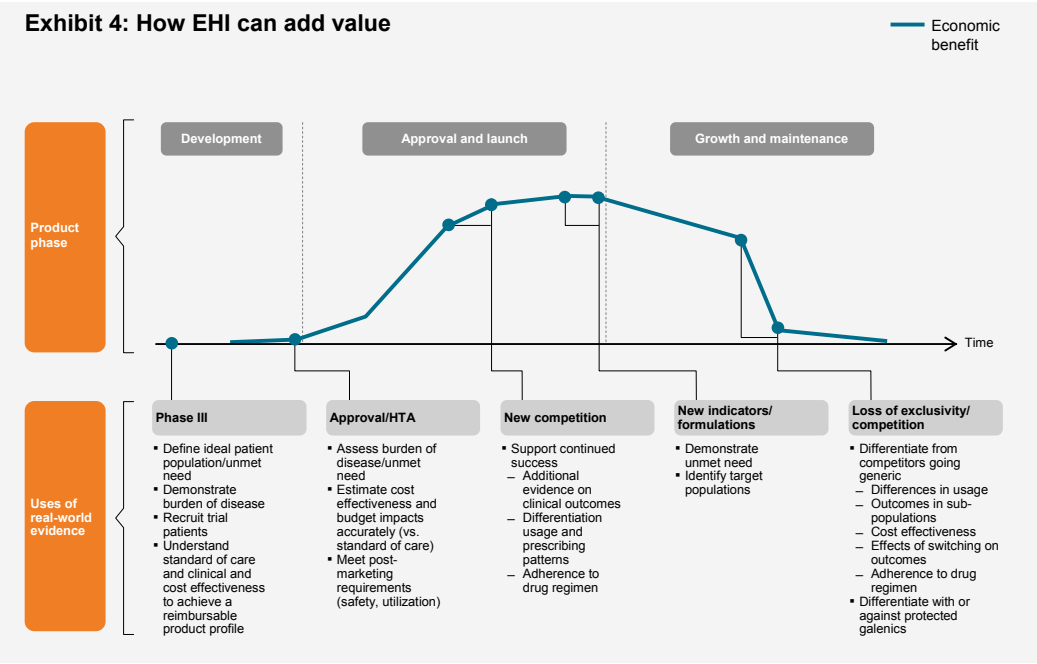


Regulators are starting to recognize that regulatory science must improve. They are also beginning to understand that a new type of dialogue with industry is needed.

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 variablized—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:

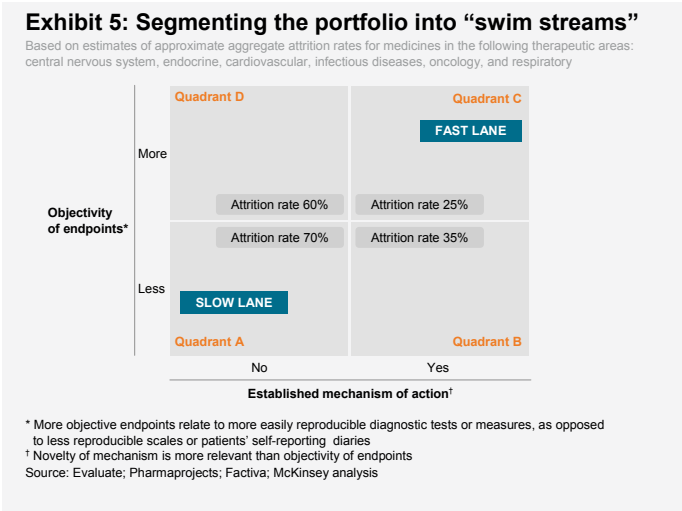
Enhance the environment you offer.

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



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 Möller** 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 Szlezak.



New frontiers in financing and collaboration

By taking advantage of a range of innovative financing and partnership models, companies can place more bets with less money, less work, and less risk. For maximum impact, they should apply these models across their whole portfolio, not on a compound-by-compound basis.

Eric David, Amit Mehta, Troy Norris, Navjot Singh, and Tony Tramontin

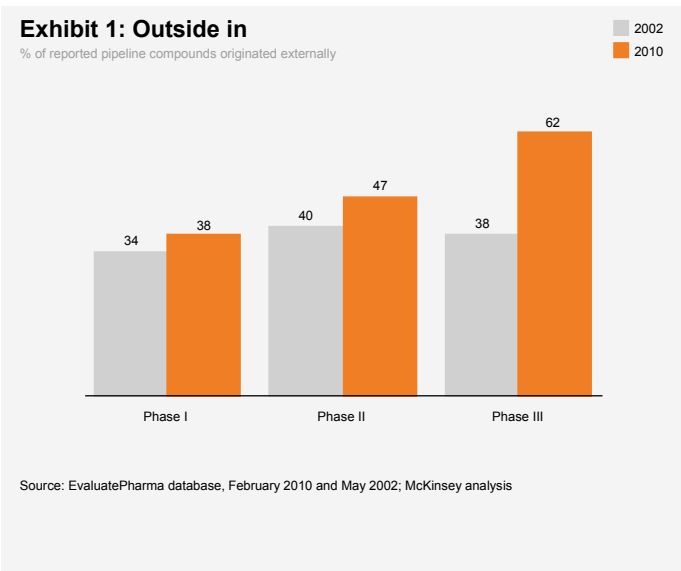
It's no secret that the biopharma industry has been grappling with diminishing R&D productivity. R&D investment more than doubled over the past decade, yet new molecular-entity approvals plummeted. The return on investment for a typical biopharmaceutical portfolio often does not even cover its cost of capital.

In response, industry players have embarked on a range of initiatives: in particular, externalizing more R&D to increase the number of drug projects and thus the chances of getting a major new product to market. In fact, over half of late-stage pipeline compounds are now externally sourced (Exhibit 1).

This externalization has occurred for the most part through fairly traditional models—such as product licencing, program partnerships, or company acquisitions—that favor majority control of assets and put primary responsibility for product development and commercialization in the hands of pharmaceutical companies. Structures have evolved to share the risks and rewards over the course of product development, but the split is generally proportional to the degree of resources invested and overall operating control. The proportions may change depending on the competition for an asset (the higher its perceived desirability, the greater risk

and cost a licensee is willing to assume) and the financing environment (biotechs with no financing alternative make their own compromises). But by and large, such variations haven't fundamentally changed the economics of externalization or dramatically improved the return on external R&D investments.

The challenge, in sum, is to increase the number of drug programs to which a pharmaceutical company has access—but without increasing to the same



degree the capital or resource investment required to access them. Thus a growing number of companies have begun to pursue novel financing and collaboration models that decouple resource commitments from financial investments, and day-to-day operating control from asset rights, to gain the maximum downstream reward from a program with minimal up-front risk. Corporate venture investments, for example, can provide an early look at maturing programs. Options can be purchased to licence future successful programs from companies without committing internal resources. And companies can reduce the development risks of internal programs while retaining control and potential for financial upside by partnering with contract research organizations, companies in low-cost countries, or private-equity investors to lower development costs, leverage external capacity, and share financial risks (Exhibit 2).

By and large, these models presuppose that much of a deal's value comes from having preferential rights to a program—and preferential access to the information needed to decide whether to exercise those rights—rather than day-to-day operational responsibilities and the associated commitments of resources and management time.

But with so many alternatives available, which models should a company apply,

Exhibit 2: A broad approach

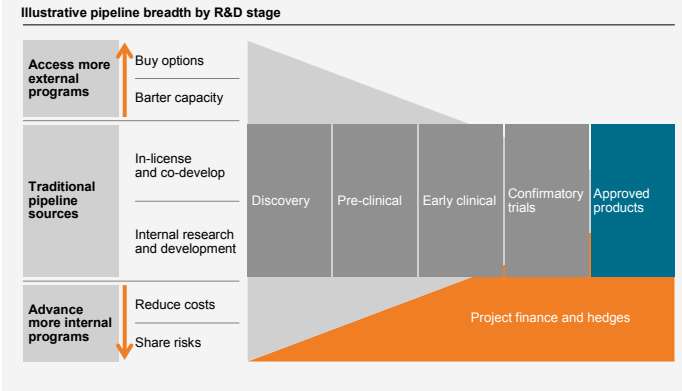
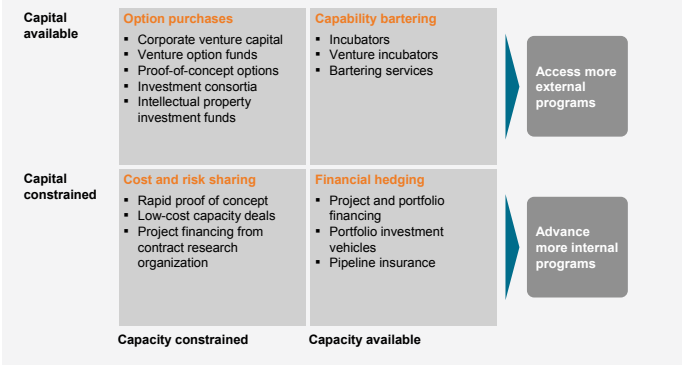


Exhibit 3: Choosing R&D financing and partnership models



and in which situations? Companies can and do use different strategies—sometimes concurrently, in different parts of a business—depending on their pipeline, capacity, financing, and risk tolerance. Exhibit 3 provides a simplified framework for deciding between innovative models, with axes representing strategy's two basic parameters: operating capacity and the availability of financing. A company with plenty of capital to invest but an extremely busy preclinical group, for example, might sign early-stage option deals: the external partner does most of the work through to proof of concept, at which point the pharma company

can exercise an option to licence the program. By contrast, if a company has sufficient late-stage development capacity but could not weather the cost of multiple late-stage product failures, it may want to enter into a portfolio insurance contract to cushion the financial risks.

Although companies ultimately make such decisions on a compound-by-compound basis, the implementation of these alternative R&D investment approaches has the greatest impact when applied across an entire portfolio to balance the overall risk/reward profile for a company and its investors. A company could, for example, finance high-risk late-stage programs externally to free up capital in order to purchase options on early-stage programs. But companies can also apply these tools selectively to fine-tune the risk/reward profile within segments of a portfolio, thus enabling them to respond more flexibly to market opportunities or perceived price/value gaps. A company could partner to access capacity and financing in a capacity-constrained disease area, for instance, while leveraging latent capabilities in other parts of the organization to incubate early-stage companies struggling with the ongoing financial crisis.

It's important to recognize that while these models can help companies to allocate capital and development resources more flexibly, and in some cases to cut operating and capital costs, they will enhance R&D portfolio productivity only if they deliver additional successful programs at lower cost or risk. No matter how small the additional investment, advancing more failed programs will drag down portfolio returns. Innovative financing and partnership approaches can improve a program's financial-risk profile but won't

drive value unless they are based on sound technical and clinical decision making.

Purchasing low-risk options

Let's start at the upper-left corner of Exhibit 3's four-box framework: risk capital available on reasonable terms but operating capacity constrained or expensive. The aim here is to create options to access promising programs with the lowest possible up-front commitment of money or resources. By applying different venture-like models, companies can get more information about available external opportunities and gain a preferred position for partnering with or acquiring the most attractive assets.

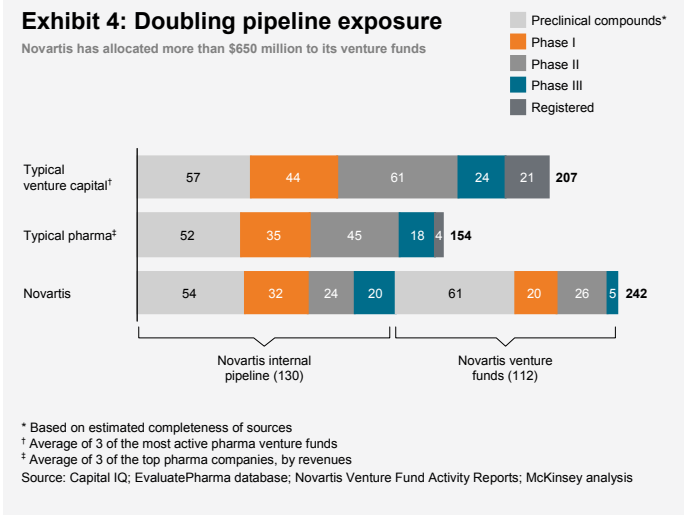
Among these models, corporate venture capital has the longest history. A number of pharmaceutical companies have created venture arms in hope of enhancing deal flow and gaining preferential access to attractive compounds. During the five years leading up to 2007, corporate venture capital represented more than 15 percent of all healthcare venture funding. While the financial returns from corporate venture capital have been buffeted along with the broader market, these investments are generally recognized to contribute strategic value to R&D portfolios.

Leading bioscience venture capital firms are exposed to more compounds, with a lower investment per compound, than the largest global pharmaceutical companies, which could similarly enhance their portfolio exposure through venture investments. Since 1996, Novartis, for example, has nearly doubled its pipeline exposure by allocating over \$650 million—10 percent of its annual R&D budget—to its venture funds

(Exhibit 4). These venture investments are made mainly through the original Novartis Venture Fund and the Novartis Option Fund, focused on securing options to specific programs. Through these investments, Novartis can gain access to information about the products of portfolio companies and seeks to couple its investments with options on rights to future products.

Other companies have pursued a more direct option-based model: they make up-front payments in exchange for rights to specific programs after proof of concept. GlaxoSmithKline, for example, faced constrained resources for traditional early-stage development partnerships and wanted wider access to scientific talent and opinion. It set up its Center of Excellence for External Drug Discovery in 2005 to create options to in-licence programs following proof of concept while keeping up-front research funding, commitment of nonfinancial resources, and day-to-day governance responsibilities to a minimum. In five years the center has produced nine ongoing collaborations and successfully transitioned three assets at clinical proof of concept into GlaxoSmithKline for further development. This option approach complements the equity investments made by GlaxoSmithKline's venture arm SR One and supplements the company's disease-focused internal discovery groups.

A third variation on these early-stage options involves newly emerging investment consortia and intellectual-property investment funds. In 2009, for instance, PureTech Ventures created



Enlight Biosciences, which is pursuing a precompetitive model for developing breakthrough technologies that could make early drug development more successful. As corporate investors, Eli Lilly, Merck, Novartis, Pfizer, and Abbott have the opportunity to invest in new technologies and have so far committed over \$70 million to Enlight. Two UK-based funds, IP Group and Sloane Robinson, have licenced pools of intellectual property from universities, advanced the technologies to preclinical proof of principle, and then licenced them out or formed new companies around them. By investing in or partnering with such funds, pharmaceutical companies can access early-stage technologies and development programs with less risk.

Bartering capabilities

Moving clockwise around the square in Exhibit 3 to the upper-right quadrant of our framework, you will find companies that have capital and at least some excess early-stage operating capacity. The goal for them is to use internal staff, knowledge, and platforms to gain

preferential access to external programs. Pfizer has set up a venture incubator that provides lab space, scientific resources, and management infrastructure to early-stage companies in exchange for preferred rights to their technologies or programs. Biogen Idec and Amgen have each committed substantial sums (\$200 million and over \$100 million respectively) to their corporate venture arms and are directing venture investments toward early-stage incubators. Amgen Ventures was a founding investor in Accelerator, which invests in early-stage opportunities for which Amgen provides access to its own facilities, scientists, management services, and vendors. Biogen Idec's Innovation Incubator (bi³) supplements the company's New Ventures arm by providing emerging companies with lab and office space, scientific input, business support, and seed financing in exchange for option rights to future development candidates.

Occasionally, pharmaceutical companies may have excess capacity, latent capabilities, or intellectual property that could be bartered in lieu of cash for preferential rights to new-product candidates. Rather than licencing or acquiring a novel target outright, for example, a pharmaceutical company may be able to contribute compound libraries, along with screening and lead-optimization capabilities, and gain product options in return. Through this services-bartering arrangement, the pharmaceutical company more fully utilizes its valuable infrastructure and gains downstream product rights, while its partner retains near-term operating control over the program and ownership of any assets not optioned by the pharma company.

Sharing development costs and risks

The lower half of Exhibit 3's four-box framework focuses on alternative investment strategies when capital is relatively tight. Many companies face declining annual cash flows that limit their ability to invest in internal programs. The strategic response is to find ways to lower development costs, access external capacity, and share the financial risks of development, while retaining downstream control of product rights. These innovative risk-sharing models enhance the risk/reward profile of early development by decoupling ownership from activity, commitment from control, involvement from information, and reward from risk.

Lilly's Chorus model represents the most discussed strategy for companies looking to solve the problem of the lower-left-hand quadrant: maximizing opportunities in capital- and resource-constrained environments, especially for the riskiest programs. In essence, Chorus is designed to reduce the costs and shrink the operations required to gather enough data on a compound to make an informed decision about full development. The group, which is small and relatively independent from the main Lilly R&D organization, conducts only critical-path experiments to address proof-of-concept questions. The other necessary (but costly and time-consuming) work of early development, such as formulation, delivery, and manufacturing scale-up, comes after Chorus decides to advance a program. To date, Chorus has advanced two dozen compounds into early development, and half of the ten compounds that have completed proof-of-concept studies have advanced to full development.

This success has inspired Lilly to seek ways to replicate the model. In 2009 it created Vanthys, a joint venture with India-based Jubilant Organosys, to combine Chorus's rapid proof-of-concept model with Jubilant's lower-cost structure. With this move Lilly established a highly efficient risk-sharing path to clinical proof of concept for compounds that it continues to own. It reserves the option to keep or sell its stake in Vanthys in future.

The deal with Jubilant extends another strategy that Lilly has pursued more broadly: outsourcing to companies in low-cost countries by entering into risk-sharing partnerships. Lilly, Merck, and GlaxoSmithKline have each signed integrated drug discovery and development alliances with Indian or Chinese biopharmaceutical companies, such as Piramal Healthcare and Ranbaxy Laboratories (now a unit of Daiichi Sankyo). In these deals, the low-cost company takes on development responsibilities for specified programs through proof of concept, and then the global pharma company regains rights to the compound in exchange for milestones, royalty payments, and, in some instances, co-promotion rights in certain countries. Pharmaceutical companies can therefore advance internal programs that would not otherwise meet investment hurdles on a risk-adjusted full-cost basis.

In the run-up to the creation of Vanthys, Lilly crafted a number of deals to share the costs and risks of early-stage development with low-cost partners. In 2006, it joined with Indian API manufacturer Suven Life Sciences to bring a limited set of central-nervous-system (CNS) candidates into development in exchange for an up-front payment and milestones. Shortly thereafter, Lilly forged a broader risk-sharing deal with Piramal in which

that company is responsible for taking compounds contributed by Lilly through Phase III development in exchange for milestones and royalties. Because Lilly made no up-front payments, Piramal is in effect providing early-stage project financing for the programs, in addition to low-cost development capacity. Following this deal, Lilly partnered with Hutchison MediPharma (a division of Hutchison China Meditech), which stands to earn milestones and royalties on successfully developed products as well as gaining rights to any compounds Lilly decides not to develop.

Through these low-cost risk-sharing deals, Lilly has dramatically lowered the financial hurdle for advancing early-stage projects, enabling it to pursue more programs with fewer resources and less capital. The failure of any program would not hinder Lilly's ability to finance other important programs or reduce its appeal to investors, much less risk its viability—the challenge for much larger, more expensive late-stage programs.

In the past, partnering and spin-outs—such as Bristol-Myers Squibb's partnering of late-stage assets with AstraZeneca and Pfizer—have been the favored ways to transfer late-stage development risks. Under these approaches, however, it can be challenging for companies to retain a meaningful share of a program's value in the event of success.

The best-publicized example of a way to access late-stage financing and capacity while maintaining control of programs was a deal announced in July 2008. Quintiles Transnational agreed to conduct Phase III development for two of Lilly's Alzheimer's candidates, and TPG-Axon Capital (with a little participation from Quintiles' managed-partnership group NovaQuest) agreed to finance up to

\$325 million of development expenses in exchange for milestones and royalties on the products. Through this deal, Lilly accesses Quintiles' expertise in Alzheimer's development and transfers much of the programs' financial risks to TPG-Axon. Lilly can use the increased financing and capacity to approach Phase III development more aggressively while maintaining control over both programs and freeing up internal resources and capital for other candidates in its pipeline.

According to NovaQuest, Lilly has partnered with TPG-Axon on other, undisclosed deals with pharmaceutical companies facing similar capacity and financing constraints that would otherwise force difficult R&D investment tradeoffs. Quintiles is also entering into early-stage risk-sharing arrangements, and announced an alliance with Eisai in 2009. In exchange for milestone payments, Quintiles will part-finance and lead the development of multiple indications for six oncology products through Phase II proof of concept. Pharmaceutical Product Development (PPD) also spun off its compound-partnering business in 2010, with an initial capital commitment of about \$100 million, to help the business expand without diluting PPD's core contract research earnings.

These recent developments indicate that the sharing of project finance and risk with clinical research organizations is an increasingly viable alternative for companies to access both the capacity and the financing needed to advance promising programs.

Hedging disproportionate financial risks

Before the global financial crisis, a number of approaches were emerging to help companies share the financial risks of product development while maintaining operating and strategic control. Through these models, product developers can hedge the downside while retaining most of the financial and strategic value of success. In return, their financial partners earn a premium for taking on risk, which can be spread across other, uncorrelated investments.

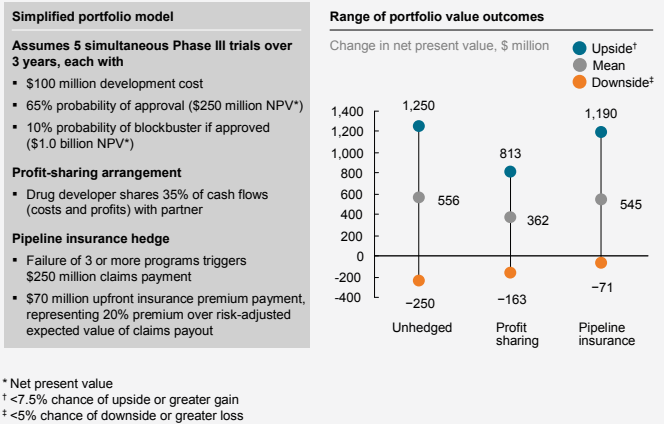
For the most part, the financial crisis has dramatically reduced the near-term ability of private-equity firms to participate in large, relatively undiversified late-stage project financings, such as TPG-Axon's funding of Lilly's Phase III Alzheimer's programs. But as financial markets stabilize and private capital returns, a variety of structures to share financial risk—such as project-based financing, pooled-investment vehicles, and even forms of pipeline insurance—will probably become available to pharmaceutical developers.

Under Symphony Capital's pioneering project-financing model, which targets small public companies that are unable to finance riskier early-stage programs, Symphony assumes the financial risk through clinical proof of concept. In a typical deal, Symphony finances the early clinical development of a portfolio of programs at a biotech company, taking ownership of them as collateral. On completion of proof-of-concept studies, the innovator can either buy back the program (if it's been successful) at a pre-negotiated time-dependent price or leave it in Symphony's hands (if it hasn't shown enough promise in the Phase II trial).

This model depends heavily on the biotech’s ability to raise buyback capital through partnerships or the stock market when a Symphony-owned product reaches proof of concept. The stock market has not always cooperated—many biotechs find that even positive data doesn’t move their shares—nor have partnerships always materialized to fund the buybacks. Largely as a result of these market forces, only two of the seven portfolios Symphony funded had been reacquired by the end of 2009. In the course of that year, Symphony altered deals with Alexza Pharmaceuticals and OxiGene, restructuring them from project financings to equity investments, because the companies couldn’t raise the cash to buy back their projects on the terms originally negotiated.

Other emerging project-financing models have also been waylaid by the market. Goldman Sachs, building on the Symphony model but targeting much larger companies, had been seeking to create a large pool of capital to finance a diversified set of early clinical programs. Some smaller companies struggling to finance late-stage programs were working with financial partners to create pooled project-financing vehicles that would enable multiple investors to finance diversified portfolios of programs under development by multiple public or private companies. These portfolio investment vehicles would theoretically allow private-equity investors to back hand-picked assets, diversify financial risks across several programs, and generate private-equity returns through a flexible range of exit alternatives. By pooling related and

Exhibit 5: Using pipeline insurance to hedge risk



complementary assets—for example, drugs to treat related conditions through alternative mechanisms—partners contributing products to these vehicles would be able to share capabilities, expertise, and infrastructure investments while accessing capital. They would hedge their program risks and still retain much of the upside from their programs.

To date, however, these financing structures have not come to fruition, publicly at any rate, as a result of the simultaneous downturn of the public markets and the decline in the number of partnerships among drug companies. These developments highlight the need for risk-sharing models that don’t depend on volatile equity markets. In the examples we’ve discussed so far, the financial partner has had to commit substantial development capital up front in return for a large share of the upside from success. For pharmaceutical companies with access to lower-cost public capital, an insurance-based model may be more widely appropriate (Exhibit 5). The idea would be not to finance any one program but to hedge against multiple pipeline failures that might threaten a company’s

viability, while retaining as much upside as possible in the event of success.

Under a pipeline insurance model pharmaceutical companies could theoretically make up-front “premium” payments to a financial partner, which would agree to reimburse them for a share of the development costs if a catastrophically high proportion of pipeline products failed. Like all insurance plans, such an arrangement would require a financial counterparty, which would be concerned about three things.

First, the risk must be easy to statistically model and thus price. Late-stage clinical-trial statistics based on therapeutic area or mechanism of action should provide a means of risk valuation that rivals or betters those used in insurance and investment banking. Second, project-specific risk data need to be easily sharable and understandable in order to minimize the risk of adverse selection; no insurer wants the drug developer to insure only the lemons. And since it's difficult to tell lemons from sweeter fruit before proof of concept, insurance markets probably won't work for early-stage clinical trials. But the risks may be more manageable in later development, where sharing of clinical proof-of-concept data makes it easier to assess risk and helps level the information playing field. Finally, the clinical program being insured would need either to follow a clearly defined regulatory path or to be pursued by an agent other than the insured developer to minimize moral hazard—the danger that the insured may withhold its best efforts from, or engage in riskier development strategies for, the hedged projects.

A suitable counterparty could then manage the risk by holding capital and diversifying or perhaps even creating secondary markets. From the developer's

perspective, these insurance contracts could preserve a program's upside while providing downside protection with a predictable up-front cost. Until such counterparties can be engaged, however, R&D pipeline insurance remains theoretical.

Overcoming organizational hurdles

Many people are talking about these strategies. Given rising attrition rates and capital costs, it's clear that drug companies must access more opportunities without increasing to the same degree the resources—cash and operations—they require. But most companies haven't yet taken meaningful steps toward implementation.

Management teams rightly resist depending on high-cost private equity or sharing future product revenues. But as a result, they often implicitly accept costs and risks across their R&D portfolio without fully assessing the opportunity cost of constrained capacity or the broader potential risks of financial distress. A thorough portfolio review often identifies areas where risk sharing and financial hedges can help balance skewed operating and financial risks.

Such deals aren't easy for investors either, particularly given the financial crisis. Even in good times, they resist buying into poorly diversified deals; what they want is a market basket of programs, or even opportunities to invest in an entire disease area or a business unit's pipeline. As far as possible, pharmaceutical companies will need to designate broader sets of compounds for inclusion in financing deals.

They must also address another important concern: transparency. Investors will worry that pharmaceutical companies



won't be completely forthright about the risks of their programs. To build trust, management teams must therefore support thorough due diligence, just as they would expect it themselves. They'll also have to explain their motives for wanting to share particular risks, and be willing to share fair value in exchange.

There are other internal challenges too. Many executives hesitate to externalize R&D responsibilities as much as these approaches require. The frequent argument against doing so is the poor quality of externally managed development programs. Often, however, executives fear giving up control. Many of these ideas—in particular the early-stage option programs—require them to shift control at least of early-stage development to a partner in return for getting, inexpensively, the information they need to reach good decisions about whether to commit their company to much more expensive downstream development.

Organizational goals must therefore be aligned with these strategies. The mandate of R&D leaders can be broadened—for example, as it is in GlaxoSmithKline's Center of Excellence for External Drug Discovery—to encompass internal and

external R&D investments. Substantial commitments can be made to separate organizational entities empowered to pursue more aggressive external approaches, as Lilly and Novartis do.

Meanwhile, executives charged with implementing these novel approaches will make mistakes, at times giving up outsized gains in exchange for hedging risks. Given the heightened career risks, companies must give managers incentives to take them. Appropriate amounts of capital should be allocated to these initiatives, for example. Leaders of initiatives should be rewarded for achieving activity-based objectives such as deals completed, amounts invested, term sheets negotiated, or due-diligence processes completed. These short-term targets should then be balanced by longer-term value-based incentives tied to investment performance and outcomes across a portfolio of programs.

Since investors have backed off, the financial crisis has given companies an excuse to ignore many alternative financing strategies that they should consider. But as financial markets stabilize, private capital will again become available to finance and share the risks of development

programs. Lest companies risk missing opportunities to apply these innovative structures, they should prepare today by evaluating portfolio risks and opportunities while building relationships with potential financial and operating partners.

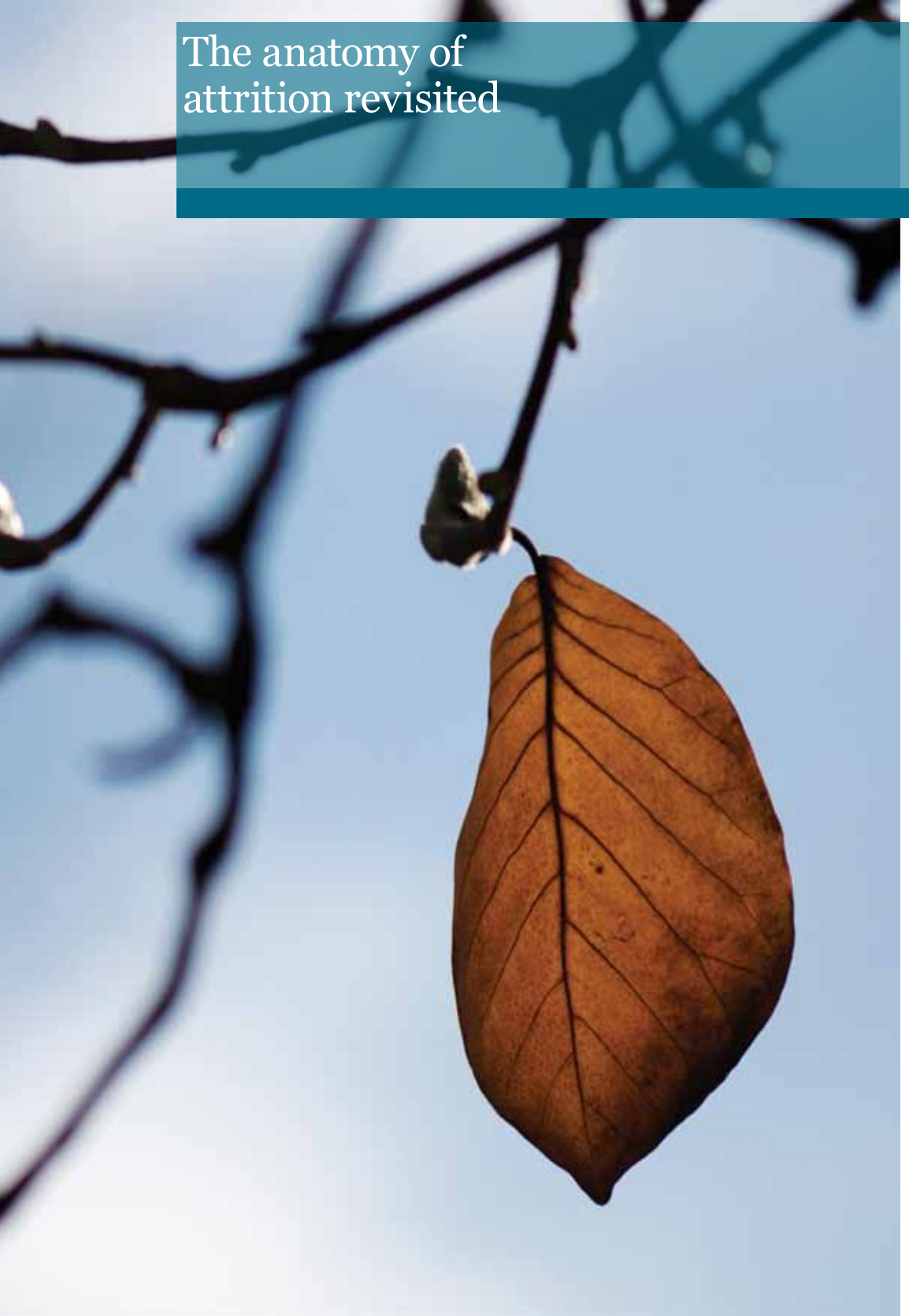


Although a few pharmaceutical companies have made strategically important commitments to one or more of these innovative financing and partnership models, most haven't moved beyond the experimental stage even with one. But the yes or no outcome of most clinical programs requires a portfolio approach to measure success and distinguish the quality of deal making from the outcome of individual programs. These strategies don't lend themselves to perpetual pilot exercises, so companies must apply them at scale to make a meaningful impact. Companies that learn to use a range of innovative financing and partnership models efficiently and flexibly across portfolio stages and business units will maximize the number of R&D programs they can advance and thus transform their overall R&D productivity.

This is a revised version of an article first published in the November 2009 edition of *In Vivo: The Business & Medicine Report* and subsequently included in the February 2010 issue of *McKinsey Quarterly*.

Eric David is an associate principal in McKinsey's Silicon Valley office; **Amit Mehta** is a consultant and **Navjot Singh** and **Tony Tramontin** are principals in the New York office; **Troy Norris** is an alumnus. The authors would like to acknowledge the contributions of Roy Berggren, Ajay Dhankar, Maria Gordian, Philip Ma, and Rodney Zimmel.

The anatomy of attrition revisited



An update of our 2010 study reveals that the steep decline in R&D success rates continues. Small-molecule pipelines have shrunk for the first time, partnered molecules are no longer stars but remain better bets than home-grown assets, and big pharma has declined faster than the industry overall.

Matthias Evers, Jennifer Ferrara, Usoa Garcia-Sagues, Mateusz Kus, Martin Møller, Jessica Ogden, and Katarzyna Smietana

More than 90 percent of compounds that enter Phase I trials are destined to fall out of the development pipeline. Although the downward trend observed over the past decade was briefly interrupted by an upward spike,¹ our latest analysis reveals that the improvement was not sustained.

To update our research, we conducted an outside-in analysis of pharmaceutical R&D attrition rates between 1996 and 2010. Using publicly available data, we tracked more than 7,000 compounds through each phase of development, including small-molecule drugs as well as biologics, but excluding drug reformulations (see the sidebar “Methodology”). Tracking

phases rather than full projects enabled us to assess trends in more detail.

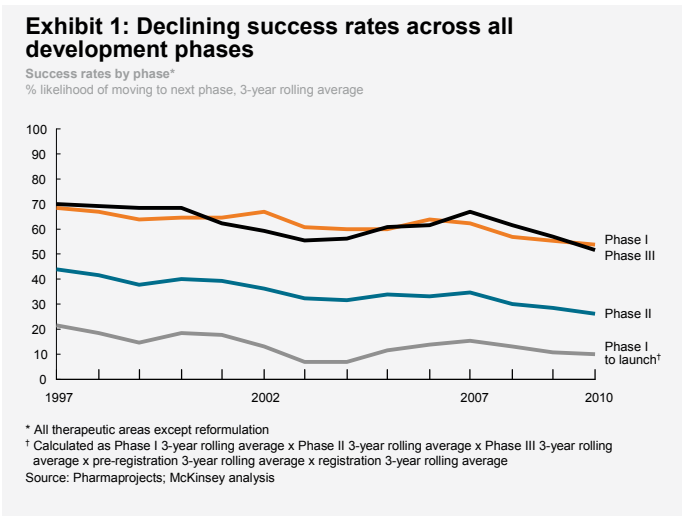
Here are our main findings:

Success rates are declining for the whole industry, and more steeply for small molecules than for biologics

Across the industry, the success rates of drugs fell between 1996 and 2010 (Exhibit 1). Although all phases were affected, Phase II continued to be the hardest hit. The upward trend observed in 2005 to 2007, most markedly in Phase III, has since reversed. If we look at the success rates for Phase I to launch and compare the three-year average for 1996 to 1998 with that for 2008 to 2010, we see a decline from 16.5 to 5.8 percent for small molecules, and from 21.7 to 10.4 percent for biologics.

The global pipeline has stopped growing

Although the number of biologics in Phases I to III continued to rise at a high single-digit compound annual growth rate from 2009 to 2011, the small-molecule pipeline shrank for the first time between 2010 and 2011, by nearly 2 percent. The shrinkage was driven



Methodology

We conducted an outside-in analysis of pharmaceutical R&D attrition rates over the 15 years from 1996 to 2010, tracking the phases of more than 7,000 compounds in development.* Our research included small-molecule drugs as well as biologics, but excluded drug reformulations. We used data from Pharmaprojects rather than companies' self-reported data.

A drug was classified as having “failed” if the trial ended early (unless it ended early because of strongly positive results), or if the trial failed to produce the results that would ensure drug approval, or if there were no reports of ongoing development for more than two years.

The analysis began tracking the phase success of a compound only after it entered Pharmaprojects, rather than including it as a success in earlier phases. This prevented the overcounting of successes in earlier phases. Each phase of each project was tracked and analyzed separately on the basis of the year it ended that particular phase (the “exit year”). By tracking phases rather than full projects, we were able to look at composite attrition numbers for the industry that reflected recent developments. This allowed for a more detailed assessment of trends over time than can be achieved by other analytical approaches, which tend to be limited in sample size.

The analysis is purely retrospective and makes no attempt to predict future trends, which are driven by factors not easily modeled on the basis of historic data, including regulatory changes, portfolio decisions, market access issues, and scientific evolution. Benchmarking therapeutic areas within individual companies, or even benchmarking small companies as a whole, is not always meaningful because of low sample size.

Our attrition database allows us to carry out other tailor-made analyses by company, therapeutic area, disease indication, or mechanism of action.

* The number of compounds has increased since our previous analysis published in 2010, which included more than 3,000 compounds, to reflect the inclusion of new drugs since 2007 as well as improved retrospective coverage from Pharmaprojects.

by a decline in products in Phases I and II, although Phase III continued to grow. This trend was observed across all therapeutic areas except oncology.

Cycle times appear to have bottomed out across phases

Time per clinical phase remained relatively stable between 2008 and 2010 for successful drugs, at around 1.6 years for Phase I, 3.2 years for Phase II, and 2.8 years for Phase III. Unsuccessful drugs are removed from the pipeline more quickly than they used to be, but they still spend more time in phase than successful ones.

Partnered compounds are maintaining their lead over “organic” compounds

Compounds developed in partnerships remain more successful than “organic” compounds (those being developed only by the originator). In 1997 to 1998, the Phase I to launch success rate for a partnered product for the top ten pharmaceutical companies was 27.2 percent, compared with 15.9 percent for an organic compound. By 2009 to 2010, these rates had declined to 5.3 and 3.4 percent respectively, with partnered compounds maintaining their lead.

Big pharma has lost its advantage

Success rates have declined more sharply for the top ten companies than for the industry as a whole. A new finding from our updated analysis is that in 2009 to 2010, the success rate for top companies dipped below the industry average, with a Phase I to launch success rate of 4.1 percent as compared with the industry rate of 5.5 percent. This underperformance was evident in all clinical phases.



Our updated attrition analysis indicates that cumulative success rates for Phase I to launch have fallen by more than 50 percent in the past decade. Although pharmaceutical companies are starting to take a more qualitative approach, remnants of the old quantitative “shots on goal” paradigm may persist in the portfolio for some time, causing high attrition to continue for several years in later phases.

Note

¹ See the results for 2005–2007 discussed in “The anatomy of attrition,” *Invention reinvented: McKinsey perspectives on pharmaceutical R&D*, McKinsey & Company, 2010, pp. 56–62.

Matthias Evers is a principal in McKinsey's Hamburg office, **Jennifer Ferrara** and **Jessica Ogden** are consultants in the New Jersey office, **Usua Garcia-Sagues** is a consultant in the London office, **Mateusz Kus** and **Katarzyna Smietana** are consultants in the Polish Knowledge Center, and **Martin Møller** is a principal in the Copenhagen office.

Managing the health of early-stage discovery



Productivity in the laboratory can be boosted by adopting best-practice behaviors in five critical areas: talent, collaboration, problem solving, project management, and strategy. Although the behaviors are not new, few research organizations are addressing them systematically.

Ajay Dhankhar, Michael Edwards, Mubasher Sheikh, Daniel Simon,
and Tony Tramontin

Productivity remains a critical issue for biomedical research.¹ Industry managers have tried to improve research productivity in various ways, including reorganization, refocusing of therapeutic area investments, and investing in new technologies. These top-down approaches have delivered variable success.² In our view, research managers should focus equally on bottom-up approaches, at the level of the productivity of each researcher.

To understand what drives major differences in productivity between research laboratories, we interviewed selected leaders of some of the world's top research institutions. We found that they largely share a common set of more than 60 behaviors that are similar across academic and industrial laboratories, regardless of research area. We then surveyed more than 4,300 researchers in 247 laboratories to explore the extent to which these behaviors correlate with laboratory performance (see the sidebar "Methodology" for details of our research methods).

Critical success factors

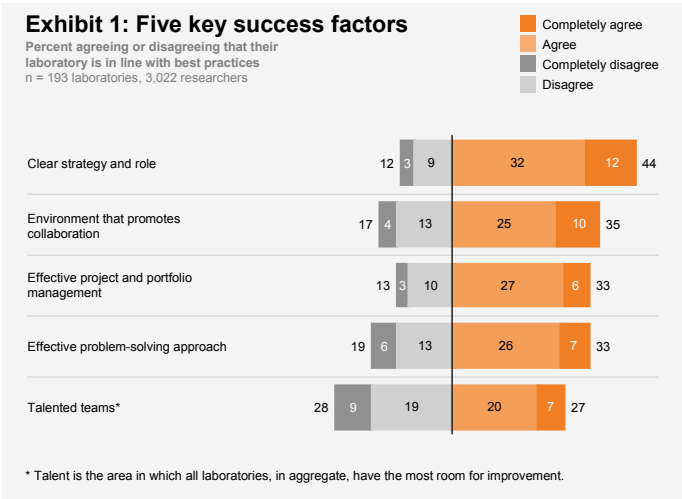
The most productive laboratories share a core set of behaviors, regardless of the research area and whether they are

in academic institutions or in industry. There is a correlation between productivity and these behaviors, which fall into five areas: talent, collaboration, strategy/role, portfolio/project management, and problem solving. Although these behaviors are not new, many research organizations are failing to address these important productivity drivers in a systematic way.

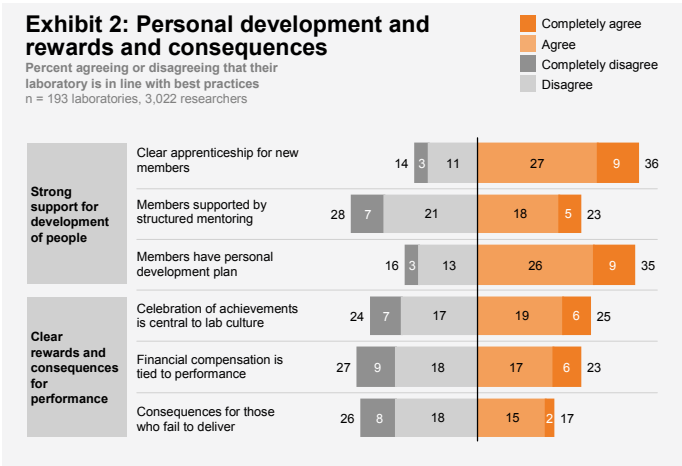
Talent

Talent is the area that is most strongly correlated with laboratory performance ($r = 0.80$; $p < 0.01$ for this and all subsequent correlation coefficients quoted). It is not simply about attracting the best people, but also actively managing their careers. High-performing laboratories get more aspects of talent right than any other practice. Despite this, only 27 percent of our respondents agree or completely agree (referred to in the remainder of the article as "agree") that their laboratory is in line with best practices: this was the lowest proportion of respondents for any of the five behaviors (Exhibit 1). Having clear rewards and consequences for performance, a focus on personal development, and a rigorous recruitment process are most important.

The best laboratories reward certain achievements—for example, an exceptional piece of research or publication in a leading journal—through either



addition to apprenticeships for new joiners. We found that 36 percent of laboratories offer apprenticeships, but only 23 percent offer longer-term mentoring. The best laboratories involve their teams in the recruitment process too: for example, by asking applicants to work in the laboratory for a trial period, and then soliciting input on the hiring decision. Although 39 percent of laboratories involve their teams, only 22 percent then give their teams a say in whether the candidate gets an offer.



For more details on best practices in managing talent in a research context, see “How the best labs manage talent,” pp. 34–8.

Collaboration

The best laboratories collaborate broadly to maximize the chances of solving a problem ($r = 0.72$), and encourage the exchange of ideas, both internally and

recognition or financial payment. However, only 17 percent of those surveyed agree that there are consequences for those who fail to deliver ($r = 0.68$) (Exhibit 2). In top laboratories, poor performance is not tolerated for long and underperformers are asked to leave if they do not respond to efforts to improve their performance. Staff turnover also ensures a fresh inflow of talent and ideas.

The best laboratories require all researchers to have personal development plans that are reviewed annually. They also offer structured mentoring, in

externally. After strategy, collaboration is the area in which laboratories do best in our analysis (Exhibit 1). Internally, good collaboration practices maximize contact between teams, which accelerates the exchange of ideas and problem solving. However, only 44 percent of laboratories agree that they encourage a sharing culture and 70 percent agree that they use regular meetings to improve collaboration. External collaboration can be a valuable source of ideas and can bring in a wider group of researchers to tackle the biggest challenges. Our analysis showed that 38 percent of

Methodology

First, we interviewed 15 of the world's leading academic researchers in biology, chemistry, and physics to understand qualitatively how they organize and manage their research and which behaviors differentiate their laboratories. We also tested these findings through interviews with leading industry laboratories.

A survey was then developed based on 60 specific behaviors identified in top-performing laboratories. An example from talent is "public or group celebration of achievements is central to lab culture and given lots of attention," and from collaboration, "there is a strong culture of sharing data, hypotheses, and results in the lab." The survey questions assess to what extent respondents believe their laboratory adheres to these behaviors. The 60 behaviors combine into the five critical success factors in Exhibit 1.

In addition, respondents' scores were linked to the performance of their laboratory. For individual academic researchers, self-assessed lab ranking and publication productivity were used, with h-index score/years used for academic laboratories. Measuring productivity output in industry is less easy for reasons of confidentiality and because there is no simple objective method available for comparing laboratories. Some laboratories are purely research- and innovation-focused, while others provide them with services or technologies (for example, high-throughput screening or DMPK testing). These require different productivity and output measures. Industry respondents were asked to self-assess and rank their laboratory's performance relative to other laboratories both internally and externally to give a directional sense. Results were averaged and used to rank laboratories.

A preliminary survey was piloted with 296 former PhD students to explore the link between scores for the behavior and productivity of a laboratory. This demonstrated a correlation between behavior scores and laboratory productivity based on group publications each year ($r=0.37$). The average score on a scale of 1 to 5 for laboratories ranked in the top 1 percent was 3.4 per behavior, versus 3.0 for laboratories ranked in the top 10 percent, and 2.5 for labs in the remaining 90 percent. This survey was then expanded: a database of responses was collected via an online survey from 247 laboratories that elected to participate, averaging 16 researchers per lab, in 18 organizations, covering over 4,300 researchers, laboratory heads, and technicians.

The correlation between laboratory behavior scores and laboratory performance was then analyzed. Laboratories for which self-assessed laboratory performance data was available were used (99 laboratories comprising 2,276 researchers). Average responses to each question for each lab were aggregated to compare what percent of labs agree versus disagree for each behavior (193 laboratories comprising 3,022 researchers).

Finally, the 10 highest- and lowest-performing laboratories were evaluated within each organization for which self-assessed lab-performance data was available. Laboratories were ranked and the number of behaviors each laboratory excelled at or needed to improve was counted. If a behaviour scored greater than 15 percent above the mean it was categorized as "excel," and more than 15 percent below as "improve performance."

laboratories encourage attendance of external events, but only 22 percent encourage external collaboration.

The best laboratories do both; for example, by drawing on relationships with groups headed by alumni.

Strategy/role

Top laboratories have a clear strategy ($r = 0.79$) and a definition of their role in the broader strategic research goals of their organization. They use this to make better day-to-day decisions; for example, how to allocate resources and/or which new capabilities to build. The strategy applied by a laboratory should create a transparent and common understanding of the major scientific problems that the laboratory is trying to solve, and the areas in which it is, or will be, distinctive to deliver solutions. The best laboratories continually search for a competitive advantage through the use of emerging technologies and new equipment.

Portfolio/project management

Top laboratories apply portfolio/project management not only for managing and reporting but also for supporting innovation ($r = 0.70$). They use specific goals, deliverables, and deadlines to manage projects, with clear stage-gates and decision criteria. Progress against these is used to continually prioritize projects and the overall portfolio to optimize resource allocation. This may be counter-intuitive to the view that great science cannot be actively managed, and that researchers are best left to their own devices. Critically, strict process management is carried out in conjunction with other practices that nurture an environment where innovation can flourish; for example, by focusing researchers' time on activities that really matter and offering time and resources for personal-interest projects.

The best laboratories are keen to terminate, sooner rather than later, any project that is not showing results. They understand that continuing to provide resources to projects that are not progressing satisfactorily deprives other projects. However, only 31 percent of laboratories actually stop projects even after a decision to do so.

Problem solving

Problem solving is at the core of successful research ($r = 0.57$), yet often the time dedicated to this is insufficient. The best laboratories solve problems together and use a hypothesis-driven approach. They also ensure that researchers spend time learning from failed experiments.

In our survey, 35 percent of laboratories agree that they spend several hours a week problem solving as a group, and 51 percent recognize the value of a hypothesis-driven approach. However, only 16 percent of laboratories agree that they actively focus their researchers' time on experiment and project design, with too much time often taken up by repetitive, low-value tasks. Only 18 percent of laboratories spend sufficient time reviewing and learning from failed experiments. The best laboratories take the time to review raw data thoroughly, and may invite the head of another laboratory or team to contribute. They also share lessons learned from failed experiments more broadly within the organization.

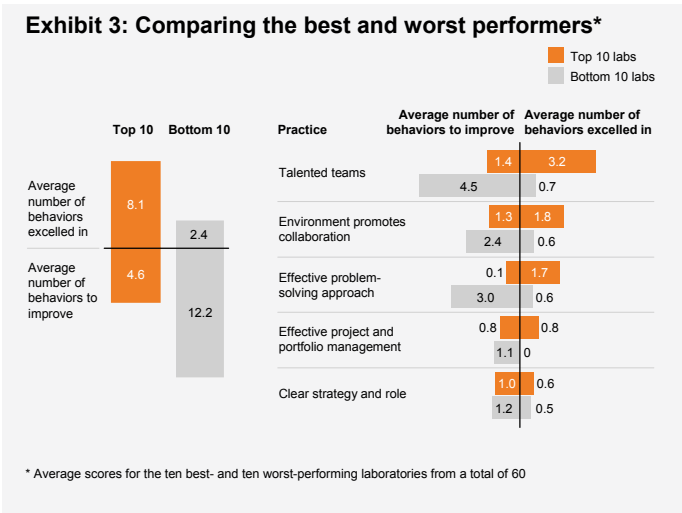
Room for improvement

Better laboratory performance is correlated with best-practice behaviors across all five of the areas we analyzed, although some behaviors matter more than others, in particular, talent. In one cohort analyzed, the top ten best-performing laboratories,

based on self-assessment, excelled in eight of these behaviors (on average), compared to the ten worst-performing laboratories, which excelled in only two (Exhibit 3). Importantly, they needed to improve in far fewer behaviors: five on average for the best-performing laboratories, compared to 12 for the worst-performing laboratories.

We analyzed the h-index³ of 290 scientists who have won major prizes between

2000 and 2010. Top-quartile laboratories in this group were at least four times as productive as the bottom-quartile laboratories. Productivity in industry is harder to measure owing to consistency and confidentiality issues. However, industry researchers seem to be overly optimistic about their performance, with 70 percent of researchers surveyed believing that they work in a top-quartile laboratory.



Our findings show that less productive laboratories often neglect the five critical areas of behavior we identified, even though they are well known. Furthermore, even the best laboratories have room for improvement. This analysis indicates there is an important opportunity to increase research productivity.

Notes

1 S. M. Paul et al., “How to improve R&D productivity: The pharmaceutical industry’s grand challenge,” *Nature Reviews Drug Discovery*, Volume 9, 2010, pp. 203–15, and E. David, T. Tramontin, and Z. Zimmel, “Pharmaceutical R&D: The road to positive returns,” *Nature Reviews Drug Discovery*, Volume 8, 2009, pp. 609–10.

2 B. Munos, “Lessons from 60 years of pharmaceutical innovation,” *Nature Reviews Drug Discovery*, Volume 8, 2009, pp. 959–68, and J. Garnier, “Rebuilding the R&D engine in big pharma,” *Harvard Business Review*, Volume 86, 2008, pp. 68–76.

3 J. E. Hirsch, “An index to quantify an individual’s scientific research output,” *Proceedings of the National Academy of Sciences of the United States of America*, Volume 102, 2005, pp. 16569–72.

This is an edited version of an article that previously appeared in the March 2011 issue of *Nature Reviews Drug Discovery*.

Ajay Dhankhar is a director in McKinsey’s New Jersey office; **Michael Edwards** and **Mubasher Sheikh** are principals in the London office, where **Daniel Simon** is a consultant; and **Tony Tramontin** is a principal in the New York office.

How the best labs manage talent



It’s no coincidence that the highest-performing labs across industries use the best talent-management practices. What matters most is recruiting for potential, nurturing people, recognizing success, and building diversity.

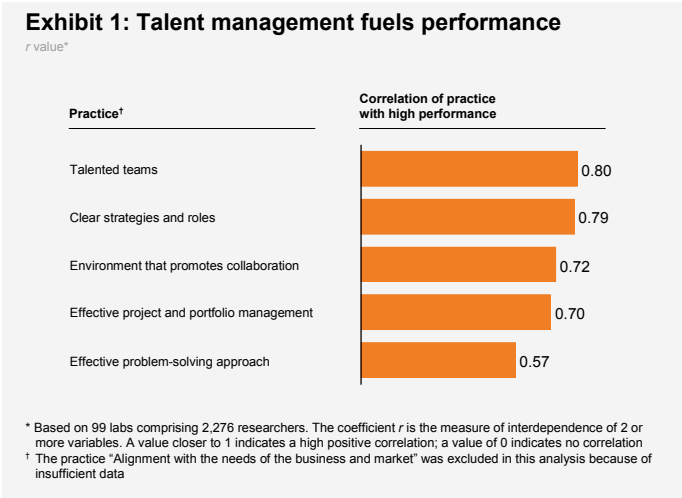
Wouter Aghina, Marc de Jong, and Daniel Simon

Of the \$1.2 trillion spent globally each year on R&D across corporations and academia, 40 percent—much the largest share—pays for people. Our team interviewed and surveyed world-class researchers in academia and a range of industries to understand what drives research productivity in labs and identify the practices and behaviors that mark out the top performers (see “Managing the health of early-stage discovery,” pp. 28–33, for more details of the research effort).

Our conclusion was that talent management, more than anything else, is what the best R&D operations consistently get right (Exhibit 1). It is the most important driver of productivity and shows the highest level of correlation

with strong performance. Interestingly, talent management also has the highest opportunity for improvement of all the practices we identified. That makes it a tremendously powerful lever to improve R&D productivity, regardless of its current level (Exhibit 2).

Top-quartile academic labs are five times more productive than bottom-quartile ones. Similar differences exist among industrial labs. Yet many research institutions don’t understand how well they are doing because the people who work there wildly overestimate their own performance: in our survey, 12 percent of them suppose that their own lab is in the top 1 percent, and 70 percent think it is at least in the top 25 percent.



Most researchers don’t know how productive great labs are or how they become great. In fact, most labs can assess how well they do only by basic output measures. A halo effect further distorts perceptions: researchers who think that their lab performs well assume that its talent-management practices are also strong.

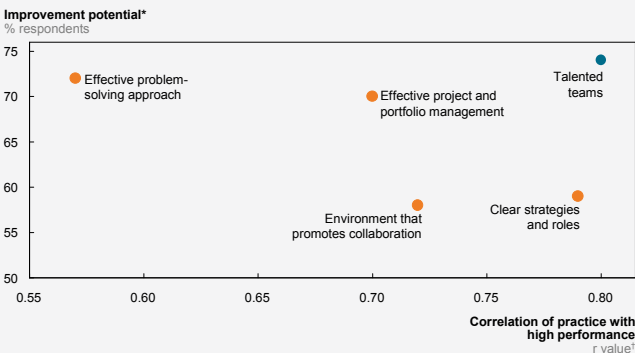
What top labs get right

Talent management isn’t simply about hiring the best; not everyone can. It’s about managing talent appropriately through selection, recruitment, development, and rewards. Just about any lab can do so, yet many don’t. We looked at each of these areas, and while all are correlated with performance, some matter more than others (Exhibit 3).

Recruiting for potential

Managing talent appropriately starts with recruiting appropriate talent. The head of a top-ranking academic lab told us that “the most important intrinsic we look for is scientific curiosity.” Great labs such as this one evaluate the potential of researchers by appraising their basic intellectual ability, general problem-solving skills, and enthusiasm. They also test a candidate’s cultural fit, which is important to support teamwork and collaboration, which in turn drive productivity. Candidates may, for example, spend an afternoon devising answers to a specific question or working in the lab with the team. This approach helps labs assess a candidate’s social compatibility as well. Before making a decision on recruitment, the best labs also solicit the views of team members about each candidate.

Exhibit 2: Room for improvement



* Defined as percentage of respondents within a lab who neither agree nor strongly agree that their lab is in line with the desired practice
† Based on 99 labs comprising 2,276 researchers. The coefficient *r* is the measure of interdependence of 2 or more variables. A value closer to 1 indicates a high positive correlation; a value of 0 indicates no correlation

Exhibit 3: Behaviors that count



* Based on 99 labs comprising 2,276 researchers. The coefficient *r* is the measure of interdependence of 2 or more variables. A value closer to 1 indicates a high positive correlation; a value of 0 indicates no correlation. Only behaviors with values > 0.55 are shown

Average labs look mostly for specific technical proficiencies—say, the ability to use a piece of equipment or to run certain tests. Specific technical capabilities are sometimes required, but even when hiring for them, top labs want people who can adapt to new roles as the research evolves. Those new roles, especially in industrial settings, should include project management and business experience—something many labs overlook.

Nurturing people

Talent management doesn't stop once researchers are hired. As an R&D executive told us, "Many of our research leaders don't have the capabilities they need to succeed in senior positions in the organization. We are trying to give people more experience across the business to round out their future leadership potential." A top lab, unlike a weaker one, actively supports its researchers' development throughout their careers. Senior team members, for example, spend significant time in solo sessions with new researchers and mentor them continually. Year-end reviews appraise these activities. The most productive labs also require all researchers to develop annual personal-development plans.

Recognizing success

Many researchers crave recognition, and labs have a number of ways to provide it: public acknowledgement in meetings, awards, and opportunities to present at conferences or to attend symposia. Even more recognition comes from giving high performers active opportunities, such as larger research budgets, leadership of bigger efforts, and part-time professorships. These incentives, our work shows, often inspire researchers more effectively than money does. They cut turnover significantly and almost always cost far less than financial compensation.

Although public recognition is important, it isn't everything: we found that researchers also want financial rewards for performance. In the best labs, such incentives are linked transparently to achievements or outcomes—great research, publication in a leading journal, the attainment of a milestone, or a successful patent application. One lab gives small cash bonuses to researchers chosen by peers for exceptional

helpfulness. Another offers stock options for killing projects early, to avoid wasting money on futile or low-value efforts. Many academic labs, however, must rely more on nonfinancial motivators.

Not everyone succeeds in the laboratory. Obviously, failure should have consequences, but often it doesn't: in one research unit, the weakest performers were moved to another lab rather than counseled to leave. The best labs don't tolerate poor performance for long. If foundering researchers don't improve, they are asked to depart, which carries the added advantage of importing fresh talent and ideas.

Building diversity

Another driver of high performance is a diverse team of people with different backgrounds, specialties, and forms of expertise to help solve problems. The most important aspect of building such a team is encouraging turnover, not only by weeding out underperformers, but also by encouraging rotation to adjacent research areas, other geographies, different roles, or, for an industry lab, to the business side of the company. To help researchers better understand the needs of business and to create a greater appetite for career opportunities outside R&D, one commercial lab organizes regular presentations by former group members who have rotated into business positions.

Room for improvement

Of all the practices that influence a lab's productivity, the researchers we surveyed told us that talent is the one most in need of improvement. Even the best labs can raise their game in this area, and their research productivity can

improve significantly even if executives are happy with its current level.

Given the importance of research for many (if not most) companies, these are clearly matters for the C-suite, not just research managers. Top executives should start by focusing on practical, tactical measures, inquiring about the research unit's diversity in background, experience, and capabilities; the ability of its culture to support innovation; the support researchers get for personal development; and the alignment between incentives and performance.

Once research leaders accept the value of initiatives to improve talent management, these are easy to implement and have high impact. What's more, their incremental cost is much lower than that of many other ways of making labs more productive—for example, reorganizing them or investing in new facilities.



Talent management is highly correlated with strong performance in research organizations, yet it also has the greatest opportunity for improvement. No lab should neglect its people.

This is an edited version of an article that previously appeared in the May 2011 issue of *McKinsey Quarterly*.

Wouter Aghina and **Marc de Jong** are principals in McKinsey's Amsterdam office; **Daniel Simon** is a consultant in the London office. The authors wish to thank Ajay Dhankhar, Michael Edwards, Mubasher Sheikh, and Tony Tramontin for their support with the research behind this article, as well as Ankita Gupta, Eoin Leydon, and Kate Smietana for their help with the analytics.



Value-driven drug development: Unlocking the value of your pipeline



Even safe and effective drugs struggle to gain regulatory approval and market access. R&D and commercial teams should adopt a new paradigm: collaborating at the beginning of Phase II to keep a laser-sharp focus on stakeholder value.

Matthias Evers, Petra Jantzer, Valentina Sartori, and Michael Steinmann

In the 1990s pharmaceutical companies could bank on a successful drug launch if they could prove that their drug was safe and effective. Since then the goalposts have shifted. Regulators want proof that new drugs are safer and more effective than those already on the market,¹ and even regulatory approval is no guarantee of success. Healthcare providers the world over are struggling with rocketing costs, making them reluctant to pay for drugs that do not deliver significant incremental benefits to patients—particularly if they come with a high price tag.

The result is that many drugs fail to secure broad market access or to earn the developers an acceptable rate of return. Between 1998 and 2008, for example, the UK's NICE granted restricted or no market access to almost 60 percent of drugs from the top ten pharmaceutical companies. Meanwhile, since its inception in 2004, Germany's IQWiG has classified 70 percent of the drugs it has reviewed as “benefit not proven.”

The market-access challenge is likely to increase as payors demand ever more value for their money in order to contain healthcare costs, which have risen twice as fast as GDP since 1970. Accordingly, pharmaceutical companies have experimented with new approaches to try to improve their odds of success. Many, like GSK and Novartis, have worked closely with payors in late-stage development; others, like Pfizer and Janssen, have done so after launch as well, through risk-sharing agreements, for example. In our opinion, however, the only way pharmaceutical companies can consistently launch successful drugs is by working to meet the market's needs much earlier in the development process.

This requires a new paradigm. R&D and commercial teams need to start working together when planning for proof of concept (PoC) in Phase II. And instead of searching for a gap in the market for the compounds they develop, these cross-functional teams need to design a compound to fill a market gap. That gap will be defined not just by the needs of patients but also by the needs of regulators, health technology assessment bodies (HTAs), and payors.

The drugs that prove successful will be those that demonstrate their value to all these stakeholders, and do so early in



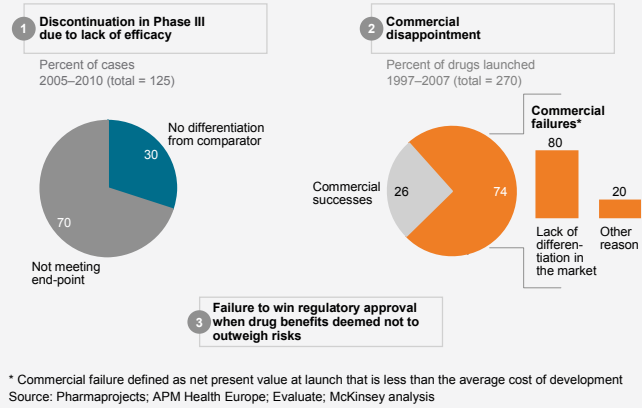
development. We call this new paradigm “value-driven drug development.” It seeks to maximize the value of a company’s current pipeline and to replenish it with new and valuable compounds by steering research in the right direction. In so doing, it helps mitigate three of the main risks in drug development: discontinuation in Phase III due to lack of efficacy; commercial disappointment (often because of lack of differentiation); and failure to gain regulatory approval because the compound’s risks are deemed to outweigh its benefits (Exhibit 1).

The four imperatives of value-driven drug development

Value-driven drug development has four essential components: understand what outcomes matter to patients and other stakeholders at least five years before launch; sharpen the focus of Phase II to define value as well as dose; upgrade team and leadership capabilities; and instill a performance culture that encourages innovation and maximizes value.

Understand what outcomes matter to patients and other stakeholders at least five years before launch
Even as early as five years before launch, the patient should be in focus. At this stage, the task is to identify, using real-world evidence, patient needs not yet met by competitors for specific indications, and to understand what profile a new compound should have to satisfy those needs. The next step is to identify a sub-set of patients who might benefit most

Exhibit 1: Value-driven drug development helps to mitigate three key risks



from the compound, perhaps because certain genetic variations respond well to it. Admittedly, segmentation in this manner restricts the size of the market for the proposed drug, but it also accentuates the potential differentiation from competitors’ compounds.

One example of a successful drug that has been narrowly targeted in this manner is Roche’s Herceptin. This drug specifically targets the 25 percent of breast-cancer patients whose cancer is related to an over-expression of the gene factor HER2. Oncology is the area in which most personalized medicine research has been conducted to date, but we believe other therapeutic areas are suitable too.

Efforts to differentiate a compound and so demonstrate its value can go further still by clearly defining different components of the overall outcome that the sub-group of patients would most value. For example, beyond its efficacy, a compound might also improve a dialysis patient’s quality of life by reducing the number of hospital visits required.

Increasing collaboration

At the end of 2010, the EMA launched a pilot project with healthcare stakeholders from six European countries (France, Germany, Italy, the Netherlands, Switzerland, and the United Kingdom) to assess the therapeutic and economic value of new drugs at an early stage of development, and to share their views with pharmaceutical companies. AstraZeneca, GlaxoSmithKline, and Johnson & Johnson are involved in the pilot, which currently focuses on drugs to treat type 2 diabetes and breast cancer.

Since early 2011, the EMA has also been collaborating with the European Network for Health Technology Assessment to understand how risk/benefit data contained in European public assessment reports for centrally authorized drugs can be used in HTA assessments.

In addition, regulators and HTAs are collaborating at national level. In the United Kingdom, NICE and the Medicines and Healthcare Products Regulatory Agency launched a pilot program in 2010 to give pharmaceutical companies independent scientific advice from each agency on how to design drug-development programs that would suit both of them. Although there have been no participants in the program as yet—something NICE attributes to the strict application criteria—many companies have expressed an interest.

In Sweden, the Dental and Pharmaceutical Benefits Agency and the Medical Products Agency also offer joint advice to companies that request it. Since 2009, there have been 20 such joint assessments.

After patients, the focus turns to other healthcare stakeholders that influence registration and reimbursement decisions: governments, regulators, HTAs, and payors. Stakeholders' assessments of a new drug's value will differ, as will the data they require to demonstrate that value.

Regulators are mainly concerned about the risks and benefits compared with the standard of care, and mostly require randomized control trials and "hard" clinical end-points directly related to the progression of the disease. Payors care about the total cost impact on their patient population. HTAs want to know whether the incremental benefits of a new drug can justify its cost. They may require observational and experimental studies demonstrating a more subjective

assessment by physicians or patients of the drug's impact on symptoms or quality of life. Regulators and payors are aware that their different demands can be hard for pharmaceutical companies to accommodate, and some have started to collaborate to try to reach common ground (see sidebar, "Increasing collaboration").

The development team will need to understand each stakeholder's relative influence. It used to be physicians who decided whether or not a drug was prescribed; now payors and HTAs increasingly hold sway. That said, stakeholders' influence varies by country. HTAs have little influence over reimbursement decisions in the United States, for example—that is the remit of insurance companies. In Europe,

by contrast, HTAs influence important pricing and reimbursement decisions. For example, NICE rejected the use of Genentech's cancer drug Avastin in two cancer indications (metastatic colorectal cancer and first-line treatment for metastatic renal cell carcinoma) on cost grounds, resulting in sales worth just €10 million in the United Kingdom in 2008. That compared with sales of €300 million in France, where no HTA assessment was made.

Development teams will also need to find an approach that satisfies the main regulatory agencies in the United States and Europe. It is becoming increasingly difficult to submit one registration package that works for both. For example, the EMA always requires a pediatric plan, while the US FDA does not. The EMA always requires a comparator for oncology drugs, while the FDA does not. Their assessments differ too. The FDA approved Wyeth's anti-depressant drug Pristiq while the European regulator had concerns about differentiation, prompting Wyeth to withdraw its submission.

When armed with insights into patients' needs, competitors' strategies, and stakeholders' expectations, development teams are in a position to consider their options strategically. The target product profile (TPP) sought is one that will be clearly differentiated from the future standard of care (as understood at the time of launch); one that delivers maximum value to

stakeholders; and one that carries an acceptable development risk profile.

Sharpen the focus of Phase II to define value as well as dose

Having assessed a new compound's safety in Phase I, most pharmaceutical companies focus Phase II on first understanding its efficacy (Phase IIa) and then ascertaining the right dose (Phase IIb). A few companies, such as Novartis and Wyeth, have started to do things differently in an attempt to make the development process more seamless.² We advocate an approach in which Phase II homes in as early as possible on where value might lie.

First, Phase II is used to identify the sub-set of patients who have the optimal risk/benefit profile for the compound, as described earlier. AstraZeneca recently received European approval for all lines of therapy for its lung cancer drug Iressa for a sub-set of patients with a specific biomarker—but only after it withdrew its first EMA submission following a non-conclusive Phase III study that targeted the full population of patients and went on to conduct a new, more narrowly targeted study. Its experience underscores the potential benefits of early patient stratification and the use of biomarkers in clinics.

Second, Phase II is used not just to test efficacy and dosing, but to start testing the additional questions likely to be raised in Phase III by stakeholders seeking value. In this way, the development team can quickly identify compounds that are unlikely to meet stakeholders' needs, stop development, and avoid wasting further resources. Meanwhile, compounds that remain in development have a better chance of gaining regulatory approval and market access.



Interacting with payors, HTAs, and advisory boards at this stage will help the development team test its initial hypothesis about where value lies. Input from these stakeholders will shed light on what a new compound might have to deliver to be judged better than the standard of care, which end-points need to be proven, and what data is required. Comparative studies that give an early sense of how the compound differs from the standard of care and how the pivotal Phase III study may need to be refined accordingly are also useful. Designing Phase III trials to test the compound against the likely future standard of care rather than a placebo is another means of reinforcing the compound's value.

Third, whenever possible, clinical trials in Phase II should be designed to optimize costs, time, and data quality, but without sacrificing ethical standards. Take as an example a compound that addresses a well-known and already validated mechanism. Time and costs will be saved by using an adaptive design that combines Phase IIa (proof of efficacy) with IIb (dose ranging), thereby reducing start-up times and improving dose-response estimates. The company can analyze interim results and use modeling and simulation techniques to understand the dose-response curve before continuing the trial and further refining the pharmacodynamic model. If the trial fails to demonstrate that the drug is sufficiently differentiated, the compound can be dropped in the knowledge that only limited resources have been wasted.

On the other hand, should the compound show promise, Phase III will be reached more quickly. A good example of innovation in the design of a clinical trial, one that enabled a speedy trial and ultimately faster registration, was Novartis's development

of Ilaris, a treatment for Muckle Well's disease. Novartis used modeling and simulation techniques to select the dose range, which was then confirmed in a seamless Phase IIb/Phase III trial.³

Fourth, when entering Phase II, teams need a development strategy for a mechanism of action (MoA) that addresses more than one indication. Even before PoC, a plan is needed that maximizes a drug's potential value, taking into account all the possible indications and respective patient segments. Different indications are likely to have different value profiles. They will meet unmet needs to a greater or lesser extent, carry different risks, require more or less time to develop, be priced differently, and have different interdependencies (for example, a study for one indication may reveal valuable lessons for another). All this needs to be assessed in order to understand how best to stagger development.

Upgrade team and leadership capabilities

Value-driven drug-development teams require a particular blend of skills and capabilities, as do the governing bodies that oversee them.

The team. Drug development has tended to be clinicians' turf. But if stakeholder value is the goal, other specialists need to be part of the team too.

Even at the research phase, translational science experts should be present to identify possible biomarkers and develop a biomarker strategy to help patient segmentation. Then, in Phase I, molecular diagnostics specialists should help develop companion diagnostics to measure in clinics the biomarkers identified. Strategic marketers also have a role in ensuring that market insights—such as what

competitors are up to, how other MoAs in development might compete for success, and how the market will have evolved by the time of launch—are incorporated into the development strategy.

When planning for PoC at Phase II, teams will require still more skills. The strategic-access function seeks to understand where value lies for payors and HTAs. It then works with clinicians to define the data required to satisfy hard and soft end-points, comparators, and differentiation requirements. Modeling and simulation will bring in the necessary mathematical skills not only for PK/PD (pharmacokinetic/pharmacodynamic) modeling but also for full drug-to-disease modeling or for decision-analysis support.

The team leader. By tradition, a development team is led by a clinician who has little contact with marketing or commercial divisions. But if companies want to promote a value-driven culture and operate effectively within it, a compound in development will need its own CEO: someone capable of managing a cross-functional team, aggregating its members' input, and keeping a balance between clinical excellence and successful commercialization. That calls for drug-development experience, skills in managing projects and teams, and strategic-thinking ability.

In addition, the team leader will need to establish strong knowledge networks with internal and external stakeholders and key opinion formers in order to stay abreast of research developments, monitor competitors, and be able to react to changing circumstances.

The governing body. A similar broad mix of skills and experience needs to be reflected in the governing body that

oversees the entire drug portfolio. A governing body that embraces a value-driven approach to drug development will need to have a strategic perspective on the portfolio so that it can assess the relative risk/benefit profile of any single compound within it and decide which compounds to resource and prioritize.

Like the development team, the board will need people with a mix of scientific and business skills and experience, and in particular an understanding of healthcare systems in different countries. This mix will help ensure that the board maintains a strong external focus, keeping an eye on what competitors are doing and what the market requires and providing the right guidance to development teams. In addition, the board should play an important coaching role, challenging teams constructively to ensure that their strategies are robust.

Instill a performance culture that encourages innovation and maximizes value

Value-driven drug development has a much broader exploratory remit in Phase II than current approaches do. This has repercussions: for example, because Phase II seeks to establish how far a compound differs from those that are or will be available, decisions will be taken earlier as to whether to continue or halt development. As a result, the attrition rate of projects may rise in Phase II, but could decline in Phase III. In addition, a value-driven approach may shift resources from compounds showing marginal differentiation, even if they are in large indications or segments, to those with greater differentiation but in a narrower segment of the population (for example, from hypertension to hypertension in the Afro-American population).

This exploratory approach requires a greater degree of transparency, risk-taking, and innovation. To some it may feel liberating; to others, unnerving. To support the new approach, companies need to foster a culture that treats value generation as the key criterion in all important processes.

New performance measures and incentives will help. Development teams are currently rewarded for meeting milestones on time. In the new paradigm, a team that is frank about the risks of a project or willing to make the tough decision to terminate an unpromising one because of limited differentiation will still be rewarded because it has kept its eyes firmly on the value goal. Similarly, a clinician who fails to show that a compound is different from the future standard of care but uses an innovative cost-saving trial to do so is still congratulated. On the other hand, a clinician who uses a traditional approach to avoid risks and shows mild differentiation compared with a placebo is not.

Cross-functional collaboration is key, but not easy to build. Those accustomed to working in silos tend not to like having their ideas or working practices questioned. A culture that encourages the constructive challenging of ideas and strategies will help break down silos, as will a readiness to dissent and to raise concerns when needed. Those at the

top of the organization and in positions of authority—boards and team leaders—will have to show the way. Only when they model the new methods of working will others be likely to adopt them.



To incorporate a value-driven approach capable of developing innovative drugs with demonstrated value, most companies will need to transform their entire R&D organizations. This will affect the composition of teams, governance, culture, and capabilities.

Our experience suggests that a pragmatic approach is best. Although the architecture of the transformation program needs to be clear, not every detail of the design has to be settled before the company embarks on change. Better to start quickly by piloting different elements of the program so that management can rapidly understand what works and what does not and make any necessary refinements. It also makes sense to stagger program components to avoid overwhelming the organization.

To be sure, such a transformation will stretch executives in R&D and commercial areas as well as their product teams. But done well, it will also unlock the value of the pipeline and deliver a step-change in the organization's performance.

Notes

1 One example is the FDA's tougher scrutiny of data in non-inferiority trials (for further details, see report GAO-10-798, July 2010, at <http://www.gao.gov/new.items/d10798.pdf>).

2 Novartis's approach is known as Delphi; Wyeth's as Learn and Confirm.

3 See J. Orloff et al., "The future of drug development: Advancing clinical trial design," *Nature Reviews Drug Discovery*, 2009, Number 8, pp. 949–57, doi: 10.1038/ndr3025 Perspectives.

Applying pharmacometrics in drug development



The emerging science of pharmacometrics provides powerful approaches for supporting important drug development and regulatory decisions. Applying it in clinical trials provides economic and public health benefits that far outweigh the costs.

Sandra Allerheiligen, Jogarao Gobburu, Mark J. Goldberger, Richard Lalonde, Steve Ryder, Navjot Singh, Brian Smith, and Amy Yozviak

The problem of rising drug development costs has been approached through a number of initiatives and techniques. These include pharmacogenomics, personalized medicine, and streamlining of clinical trials. Another approach shown to enhance efficient drug development decisions is pharmacometrics (Exhibit 1).

Traditionally, medical and biostatistical experts have played a central role in assuring the validity of pharmaceutical testing by formalizing the empirical analysis, summarization, and interpretation of experimental and observational data. The emerging science of pharmacometrics, which builds on physiological, pharmacological, and biostatistical principles, provides additional powerful approaches for supporting important drug development and regulatory decisions. Numerous successful case studies published by academic, industry, and

FDA scientists attest to the value of its contribution to decision making (Table 1).

Yet despite these successes, executives and managers in R&D are sometimes skeptical of the benefits of applying pharmacometrics to clinical trials. In particular, they ask if it will delay their new drug application, take a long time, or require a lot of resources to deliver. The answer to all these questions is no. In fact, the economic and public health benefits of pharmacometrics far outweigh the costs of implementing it, which are marginal compared to the final cost of a trial. In most cases, the level of effort required is as low as one person for up to six months.

Pharmacometrics can provide important information in both proof of concept and registration studies. Although several of the assessments to date have focused on evaluating and in some cases “rescuing” development programs, it should come as no surprise that designing a trial with pharmacometric objectives in mind and using these tools early in development can reduce problems and increase the likelihood of success.

The American Society of Clinical Pharmacology and Therapeutics (ASCPT) has set up a pharmacometrics task force to build momentum for the discipline and accelerate its adoption

Exhibit 1: What is pharmacometrics?

Pharmacometrics analyses are...

Quantitative analyses of data pertaining to:

- Pharmacokinetics
- Biomarkers
- Clinical outcomes
- Disease characteristics
- Trial characteristics

- Can include:
 - Mathematical modeling and simulation
 - Statistical analysis
- Often used to facilitate efficient drug development and approval process
- Needs multidisciplinary team consisting of quantitative clinical pharmacologists, statisticians, engineers, data management experts, and clinicians

Table 1: Advantages of pharmacometric analyses

Advantages	Examples
Propose best doses	Simulation of dose titration based on exposure–response was effective in identifying target trough concentration, demonstrating effectiveness and justifying Phase III studies of a drug with challenging highly variable PK between patients and high trough concentrations in Phase II studies. ¹
Estimate effect size	Pharmacometric analyses enhanced trial success by increasing study duration. ²
Rescue discarding good drug	A new dosing regimen was selected based on pharmacometric analyses and evaluated in an additional clinical trial leading to drug approval. ³
Target patient selection	Pharmacometric dose–response analysis identified that the proportion of mildly diseased non-responders was the primary cause of lack of evidence of effectiveness. ⁴
Maximize value of prior data	Approval of a drug in pediatrics was based on demonstrating similar exposure–response relationship for seizure frequency in pediatrics and adults using prior data from adjunctive therapy trials. ⁵
Drug approval	Clinical trial simulations of a drug dosage regimen based on iPTH/80 was predicted to significantly lower the rate of hypercalcemia compared to the iPTH/60-based regimen tested in clinical trials without significantly impacting efficacy, leading to drug approval without the conduct of further clinical trials in patients. ⁶
Labeling	Drug dosing regimen used in clinical trials resulted in overshooting and oscillations around the target blood pressure. Simulations of the exposure–response relationship were used to optimize the dosing regimen to quickly achieve and maintain target blood pressure. ⁷

and impact in drug development. The key challenges that pharmacometrics faces include the perception that its involvement slows drug development timelines and raises costs; the lack of awareness of its full benefits; and the lack of adequate training infrastructure.

Recognizing these challenges, the task force is focusing on some of the success factors for enhancing adoption. These include educating professionals about the cost and speed implications of pharmacometrics (acknowledging that in some cases it may prolong early-phase trials), increasing the awareness of its benefits and successes among clinical development executives and scientists,

and expanding the number of trained professionals. Initiatives under way include the creation of a pharmacometrics resource portal to build interest among faculty and students and promote training, the development of a funding source in collaboration with other professional organizations to support graduate students, fellows, and post-doctoral fellows pursuing pharmacometrics at participating organizations, and the convening of workshops and symposia. The task force is also planning to promote the value of the discipline to industry by providing a platform for sharing interesting applications of pharmacometrics concepts with decision makers from industry, regulatory bodies, and academia.

Hurdles remain, such as structurally aligning pharmacometrics within large organizations to reflect its multi-disciplinary nature and its implications for clinical decision making, and developing standardized analysis and reporting. However, it is our belief that the discipline will evolve significantly in the next few years and come to play an important role in enhancing drug development decisions.



Pharmaceutical executives and heads of R&D would be well advised to ask themselves a few key questions about the status of pharmacometrics in their organizations. Are we making full use of

pharmacometrics—for instance, to rescue drugs or modify trial design? Do senior managers have a good understanding of the role pharmacometrics might play in the drug development and review process? What benefits could we derive by making focused investments in this area? Do we have the right resources and skills in place? What are the obstacles to increasing the use of pharmacometrics in our organization?

The answers to these questions will not only provide a snapshot of the current state of affairs but also help executives use pharmacometrics to reduce problems in drug development in future and increase the likelihood of success.

Notes

- 1 Atsunori Kaibara, presentation at PK/PD Internal Symposium on Modeling and Simulation in Drug Development and Clinical Applications, Yonsei University Medical Center, Seoul, Korea, 2006.
- 2 L. Zhang, V. Sinha, S. T. Forgue, S. Callies, L. Ni, R. Peck, and S. R. Allerheiligen, “Model-based drug development: The road to quantitative pharmacology,” *Journal of Pharmacokinetics and Pharmacodynamics*, Volume 33, Number 3, pp. 369–93.
- 3 V. A. Bhattaram, B. P. Booth, R. P. Ramchandani, B. N. Beasley, Y. Wang, V. Tandon, J. Z. Duan, R. K. Baweja, P. J. Marroum, R. S. Uppoor, N. A. Rahman, C. G. Sahajwalla, J. R. Powell, M. U. Mehta, and J. V. Gobburu, “Impact of pharmacometrics on drug approval and labeling decisions: A survey of 42 new drug applications,” *AAPS Journal*, Volume 7, Number 3, 2005, pp. E503–12.
- 4 V. A. Bhattaram, C. Bonapace, D. M. Chilukuri, J. Z. Duan, C. Garnett, J. V. Gobburu, S. H. Jang, L. Kenna, L. J. Lesko, R. Madabushi, Y. Men, J. R. Powell, W. Qiu, R. P. Ramchandani, C. W. Tornoe, Y. Wang, and J. J. Zheng, “Impact of pharmacometric reviews on new drug approval and labeling decisions: A survey of 31 new drug applications submitted between 2005 and 2006,” *Clinical Pharmacology & Therapeutics*, Volume 81, 2007, pp. 213–21.
- 5 See note 4 above.
- 6 Zemplar Capsules United States package information, June 2009, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021606s004lbl.pdf (March 18, 2010).
- 7 Drug approval package, Cleviprex (cleviprex butyrate), application number 022156, approval date 8/1/2008, at www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022156_cleviprex_toc.cfm.

This article is adapted from “ASCPT task force for advancing pharmacometrics and integration into drug development” published in *Clinical Pharmacology & Therapeutics*, Volume 88, 2010, pp. 158–61.

Sandra Allerheiligen is a vice president for modeling and simulation at Merck & Co., **Jogarao Gobburu** is head of the pharmacometrics division at the Center for Drug Evaluation and Research, US FDA, **Mark J. Goldberger** is a vice president for regulatory intelligence and FDA liaison issues at Abbott, **Richard Lalonde** is global head of clinical pharmacology at Pfizer, **Steve Ryder** is head of global development at Astellas, **Navjot Singh** is a principal in McKinsey’s New York office, **Brian Smith** is a biostatistician director at Amgen, and **Amy Yozviak** is an alumna of McKinsey.



Design to value in medical devices

As price pressures increase, medical device makers need to rethink their product development processes. Design to value can help get costs under control while delivering exactly what customers want.

Sastry Chilukuri, Michael Gordon, Chris Musso, and Sanjay Ramaswamy

"If medical device companies want to continue to make money as prices face continued pressure, their only option is to take cost out." This comment from the head of procurement at a major US healthcare provider neatly sums up the state of play in the medical device industry. The sector has always been challenging, with increasingly complex technologies and tough quality and regulatory hurdles. Until recently, device makers who overcame these barriers could sell their products at prices that justified the effort, but today they are operating in a different world.

In developed countries, growth is slowing and healthcare systems are coming under severe financial pressure. Providers are responding by exploring every opportunity to increase efficiencies and reduce costs. In developing countries, on the other hand, new opportunities are arising as a rapidly growing middle class demands more medical devices of all types, although price sensitivity is acute. A sophisticated regional industry is growing to serve this demand, and ambitious new players from China and India are keen to take their low-cost designs to enthusiastic hospital buyers in Europe and North America.

The main challenge for device makers is to find new ways to maintain their competitiveness. Like the auto, consumer electronics, and telecommunications

industries before them, they are paying fresh attention to the detailed design of their product ranges. By finding opportunities to eliminate excess cost, they hope to gain the flexibility to sell profitably in both cash-strapped traditional markets and price-conscious new ones. History shows that the winners will be those that can deliver exactly what the customer wants—nothing less, nothing more—at the best possible price.

Cheaper, but for whom?

This new game is proving challenging in developed and emerging markets alike. Success in emerging markets requires a deep understanding of stakeholders' needs, which is hard to get from a design office on the opposite side of the world.

One maker of electronic pacemakers developed a low-cost device aimed at the potentially huge tier II market of lower-income customers in developing countries. By replacing the conventional programmable control with a simpler electro-mechanical version, the company dramatically reduced the cost of the device. Even so, the product failed in the market: few customers in the target regions could afford the combined cost of the pacemaker and the surgery to

fit it. Moreover, few local hospitals had the capabilities to implant the device, and those that did were suspicious of its mechanical controller, worrying that they would need to carry out expensive secondary operations if it were to fail.

The company subsequently launched a programmable device aimed squarely at the richer tier I market. Surgeons, the gatekeeper in pacemaker selection, were more comfortable with programmable devices, which they knew from their training in western hospitals. The programmable pacemaker performed much better in sales terms, capturing three-quarters of its target market.

Even companies that are close to customers can misunderstand their needs. A US maker of electrotherapy devices embarked on a clever modularization program that allowed one device to be configured in many different ways either at the time of purchase or later via upgrades as user needs changed. However, more than nine out of ten customers chose the same basic configuration, and few came back for upgrades. In the end, the modular architecture simply added cost, and the product lost out in the market to competing devices with simpler designs.

Companies that attempt to match product features and capabilities more closely to their customers' perceptions of value must answer a difficult question: who are our customers? Fragmented decision making in many healthcare markets makes it extremely difficult for companies to understand the requirements of all key stakeholders. To be selected for use, a device might have to be approved by a national or regional authority, selected by a healthcare provider, specified by a particular clinical team, and then chosen by doctors, often in consultation with

patients. Finally, the patient's individual reaction to the device may determine how successful it is in use and thus influence compliance and future selection.

Each of these stakeholders will have an incomplete picture of product attributes: payors may not understand the importance of usability in patient compliance, while a physician may be unaware of the ongoing cost of supporting a product in the field. As a result, the incentives to purchase in many medical device markets may be fundamentally different from the benefits ultimately enjoyed by end users.

Where does the value lie?

To overcome these problems, medical device companies need new tools and a new way of thinking about product design. In particular, they need to be able to do two things effectively. First, they must find ways to pinpoint the product features their customers need—and, critically, determine how much they are willing to pay for them. Second, companies must identify the most cost-effective ways of delivering these features to maximize available product margin.

This second requirement can be particularly challenging for design and engineering teams in the medical device sector. Years of focusing on extending the technical capabilities of their products with relatively little attention to design for manufacture or other cost-reducing strategies have left these teams ill equipped to uncover the powerful insights that drive cost out of their designs. They must find new ways to look at the whole product design process and adopt best practices from their own industry and beyond.

Leading-edge DTV

A number of companies are using design-to-value tools to cut costs, boost margins, and build market share. A few leading players are going a step further by using this approach to increase their margins by 20 to 25 percent across their entire product range.

To achieve this, they are doing several things differently from their more cautious competitors:

- Instead of being content with incremental improvements, they set transformational goals by using clean-sheet models to identify the lowest possible costs for a product and challenging design teams to achieve them.
- To deliver rapid impact and promote continuous improvement, they execute ideas quickly—often within a month—and identify improvements and modify features not once but throughout a product's lifecycle. They set robust targets for implementing improvement ideas and hold regular management reviews to highlight progress and remove roadblocks.
- They maintain an external perspective by understanding the needs of all decision makers and stakeholders early in the product development cycle and revisiting them regularly. They also repeatedly conduct teardowns on competing products to understand design approaches, feature packages, and cost positions. If customer insight or teardown skills are lacking, they train their staff or hire external talent.
- In addition, they work to foster internal alignment. At one company, sales staff initially resisted the introduction of a lower-cost product because of fears it would cannibalize a more expensive alternative. But once they understood that the product was aimed at a different customer tier and would provide access to a new market and a competitive weapon to defend against new entrants, they gave it their full support.
- Finally, cutting-edge companies build DTV into their organizational DNA—their management systems and culture. They encourage different functions to work closely together by setting up regular progress reviews and providing appropriate incentives. They also ensure that quality, manufacturability, and customer acceptance are always considered alongside cost. Some establish a center of DTV excellence that provides skills and support to design teams. Others use specific projects to establish a gold standard that will educate the wider organization on the power of the approach.

Some smart companies are starting to recognize that by making this link between the true cost of features and customers' perception of value, they can reliably deliver products that cost less and offer customers more. We call this approach *design to value* (DTV). By building design-to-value skills and processes into their product

development organizations, leading medical device makers have delivered gross margin improvements of 20 to 25 percent over a typical 18- to 24-month period (see sidebar, "Leading-edge DTV"). Along the way, they have exploited quick savings that have made the improvement projects self-funding. By the end of the

process, they have stronger product development functions, departments that work more effectively together, and momentum in the organization for broader product and portfolio improvements.

What customers want

For all but the simplest products, purchasing decisions involve complex and subtle tradeoffs among features. Customers can rarely articulate the value they attribute to a particular feature in isolation. Fortunately, modern market research techniques can give a good indication of how customers reach their perceptions of value.

Medical device companies operate in a complex multi-stakeholder environment that requires a tailored approach. Companies should first identify critical stakeholder segments for each stage of the product lifecycle and then define each segment's influence on purchasing decisions. Stakeholders can be divided into two basic groups: *gatekeepers* for whom a product must meet a basic set of criteria for features and cost, and *decision makers* who will actually make the final selection on the basis of the product's differentiating features.

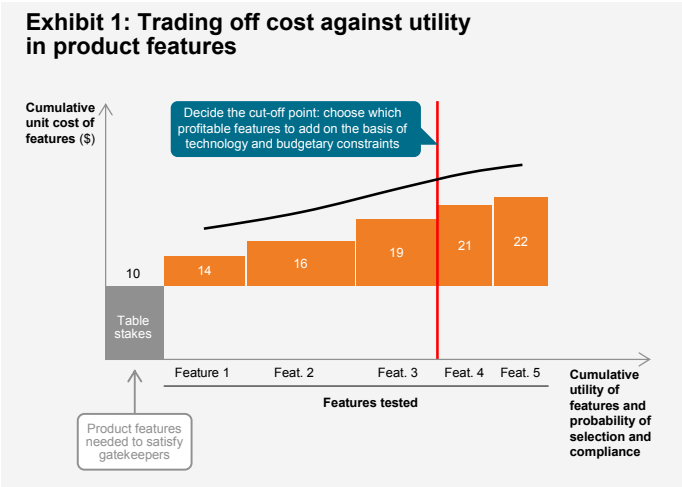
One maker of patient-operated blood-testing equipment identified four key stakeholder segments across its product lifecycle. The gatekeepers during the reseller adoption stage were the pharmacies that might choose the product and the payors that might fund it in their insurance schemes. The decision makers were the patients who might opt to use the product and the personal physicians who might influence their choice.

Representatives from all these stakeholder groups took part in interviews to help the company understand their different priorities. It found that pharmacies valued the opportunity to maximize revenues through ongoing sales of consumables for the meter, whereas payors tended to assume that all devices were equally effective and focused on the price of the device and its consumables. Healthcare providers were interested primarily in features that would ensure compliance with the prescribed testing regime; meanwhile, patients' requirements varied greatly depending on the nature of their disease.

To understand what really drove decision making, the company needed to dig a little deeper. It decided to use conjoint analysis to test various product configurations in four different customer segments categorized by the nature and severity of their disease.

Medical device companies are increasingly using conjoint analysis to navigate complex stakeholder environments and provide a rich understanding of consumer needs. In this approach, customers consider various hypothetical product configurations and price points and choose between them. Regression techniques are applied to their responses to isolate the effects of individual features on customers' perceptions of value. The results can be compellingly simple, yielding an incremental "profit" value for each of a product's features.

Conducting conjoint analyses with each stakeholder group allows companies to construct a multi-attribute utility cost curve for each stakeholder. Once a basic set of product features has been included to satisfy gatekeepers, the curve ranks each feature by the utility it provides to stakeholders and by its cost. The curve then guides decisions about



the lowest possible cost, and they overcome the limitations of conventional cost engineering by adopting a clean-sheet approach.

While many companies invest heavily in reducing product costs, companies using a design-to-value approach usually do so by examining existing designs and identifying opportunities for incremental savings. They first work to understand the likely limits of product cost reduction. Starting with a

which features to include to maximize utility and minimize cost (Exhibit 1).

A manufacturer of medical imaging equipment used conjoint studies in key customer segments to identify the factors most likely to build market share. The company found that price, brand name, and image quality were the three most important decision attributes for these customer segments. Even though the company's products already ranked among the best on the market in terms of image quality, the conjoint analysis demonstrated that a moderate increase in quality had the potential to lift market share by 11 percent. Similarly, halving downtime from four to two hours per month could increase market share by 7 percent, as could reducing the radiation dose by 25 percent, which would offer health benefits for patients.

What it really costs

The second critical element in the design-to-value equation is cost. Leading companies strive to deliver the features their customers most value at

blank sheet and using their knowledge of industry best practices for materials, processing, and labor costs, they can build an estimate of the most efficient way to deliver the desired feature set.

They then compare this clean-sheet model with current or projected manufacturing costs to gain rapid insight into the areas of design most likely to yield the greatest cost reductions. Opportunities identified in this way are often larger than those found in conventional cost engineering, since the technique encourages companies to consider changes to underlying product architecture and technology as well as individual components.

When one device maker did a clean-sheet analysis of the design of its printed circuit boards, it found it could reduce the eight separate boards in its existing design to just five, reducing the costs of the boards themselves, cutting the complexity of assembly, and allowing the product's casing to be streamlined and simplified.

Tearing it down

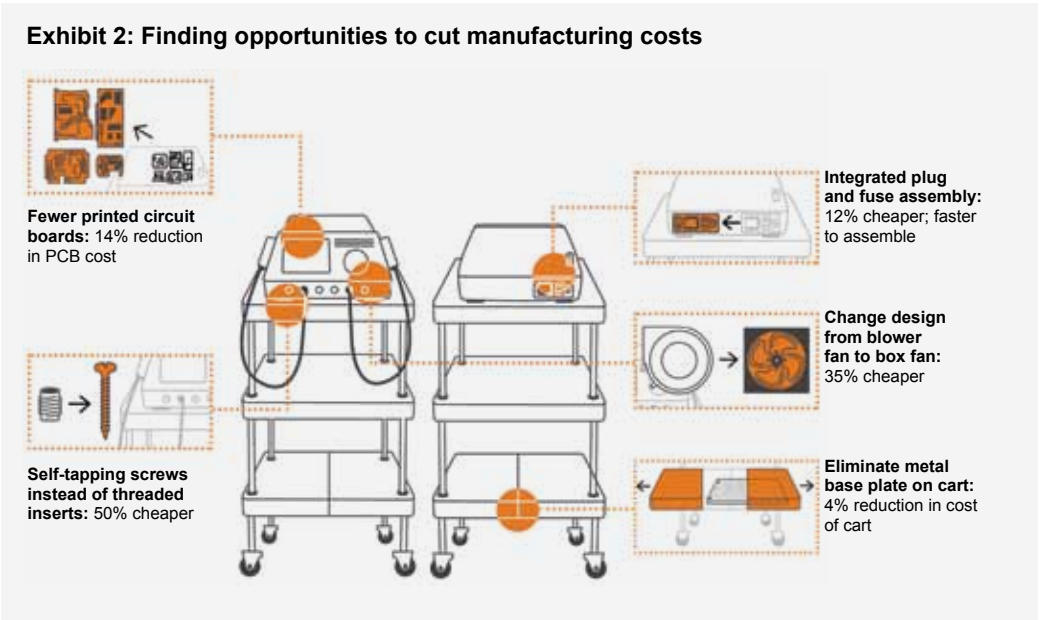
Competitive teardowns are an important activity in many industry sectors. Pulling a competitor's product apart piece by piece and comparing it with one's own is nothing new, but it continues to deliver insights into opportunities for making improvements or acquiring a competitive edge. Sectors such as the automotive industry have spent millions elevating teardowns to an art form. As competition increases and cost constraints tighten, companies in the medical devices sector are also starting to use this approach more widely.

In the design-to-value process, teardowns take on a new and central role as a vehicle for cross-functional discussions and decision making by engineering and marketing functions. When companies perform teardowns that involve everyone associated with a product—including engineering, marketing, sales, manufacturing, quality assurance, and supply chain—they can leverage all available expertise to optimize product

design. These teardowns can sometimes benefit from the involvement of suppliers too, as they may provide new perspectives on cost and functionality tradeoffs.

One company planned a series of teardowns to improve the design of a therapeutic medical device. To generate new ideas, executives invited colleagues from purchasing, marketing, engineering, and sales to see how their product stacked up against four rivals. Seeing the products together sparked an “Aha!” moment for the purchasing team, who quickly identified a series of straightforward design changes that would cut the cost of manufacture yet go unnoticed by customers (Exhibit 2).

Meanwhile, seeing how competitors' circuit boards were configured spurred the sales, marketing, and engineering teams to discuss how their company's modular approach to design was affecting manufacturing. The engineers had long assumed that being able to mix and match various features after final assembly was an advantage, and had



therefore emphasized this capability in product design. Yet salespeople reported that customers seldom ordered more than a handful of modules at purchase, or ordered more after assembly. These conversations ultimately led to simplifications in the product's circuitry that reduced purchasing costs by 23 percent.

Teardowns can be as useful with existing product lines as with new ones. For instance, one company realized it could save money by replacing the custom-made black and white LCD screen on its product with an off-the-shelf color one that was more flexible and easier to use. Comparisons of existing products often prompt a range of ideas that can be implemented quickly into the current design, as well as contributing to a "wish list" of changes for future models.

In a competitive teardown of blood-pressure monitors, one company compared its product with two rivals. In the course of a day-long session, it identified 22 separate improvement ideas that could cut manufacturing cost by 18 percent without affecting customer value. Some of the ideas were simple and easy to implement, such as reducing complexity in packaging and print materials, switching to unbranded batteries, and replacing sewn labels with screen printing. Others required more fundamental changes to the product:

eliminating printed circuit boards, reducing the size and thickness of the housing, and introducing surface-mounted components. The company also identified features that were less valuable to users and could be eliminated, such as an external power-supply connector that was rarely used on what was essentially a portable device.

Cross-functional discussions during a teardown can drive other improvements too. Conversations between sales and design at one company revealed that users found the elegant design of the product's accessories particularly appealing. By eliminating storage drawers and mounting the accessories on external hooks instead, the company cut costs and drew attention to one of the product's most compelling features at the same time.



The design-to-value approach is already helping medical device companies to gain a much richer understanding of customer needs and to meet these needs more cost-effectively. In a demanding but increasingly price-sensitive market, the ability to focus keenly on customer value can offer critical competitive advantages.

This is adapted from an article that first appeared in *Outpacing Change in Pharma Operations*, McKinsey & Company, January 2010.

Sastry Chilukuri is an associate principal in McKinsey's New Jersey office and **Chris Musso** is a principal in the Cleveland office. **Michael Gordon** and **Sanjay Ramaswamy** are alumni.

Supercharging pharmaceutical technical development



Technical development need not be a source of delay, expense, and frustration; it can be a driver of competitive advantage instead. By adopting a holistic approach rather than making piecemeal changes, companies can make big improvements in lifecycle costs and product quality.

Doane Chilcoat, Ted Fuhr, Michele Holcomb, and Jatan Shah

Imagine a world where the transition from R&D to manufacturing is seamless and swift, where processes are easily scalable, and where all the materials needed are manufacturing-safety-ready. In this world, the manufacturing process adds strength to the product's IP, and the formulation enhances market value. Process development no longer takes place in multiple rounds; instead, all changes are combined, reducing both costs and comparability issues.

Now imagine another world in which the move to manufacturing is fraught with challenges in both process and organization. Scaling up requires major rework, and R&D materials and parameters are not easily transferable to manufacturing. Formulation is unable to meet marketing specs, leading to delays. For biologics, half of early development cost is in process development, and this money is routinely invested in programs that fail in Phase I or II. Companies launch with processes they know are mediocre and have to ration supply because of lack of capacity—and that is despite investing \$150 million in improvements to a process that cost only \$20 million to develop.

Is your experience closer to the first world or the second? Different though the end states are, it takes only small changes to move from one to the other. Like the flap

of a butterfly's wings in chaos theory, an early decision in R&D may have dramatic repercussions downstream. In the first world we describe, success in operations is driven not only by high performers in the heart of the manufacturing group but also by excellence in technical development—the group at the interface between R&D and operations. In this article, we explore what it takes to be a distinctive performer in technical development and the impact this has in creating stronger, faster, and better operations downstream.

Most industries recognize that the ultimate cost and quality of a product are determined in the early stages of development and manufacturing process design. Exhibit 1 shows an example from the aerospace industry. Yet the pharmaceutical and biotechnology industries do things differently: they have traditionally locked in a sub-optimized manufacturing process that worked early on in R&D, and relied on it throughout scale-up and launch. As regulatory and economic environments become more demanding, companies will need to adopt new approaches that reduce costs, use capital more effectively, and improve process efficiency and stability.

The case for action

Many of today’s technical development practices have been driven by the prevailing regulatory paradigm, which provides incentives to avoid process changes along the development timeline and even to avoid full characterization of the process. As a result, products often make it to market with suboptimal manufacturing processes and quality levels of less than 2 sigma. In most companies, the manufacturing function is left to optimize its processes over time. The result is higher costs and risks caused by delayed product launches, issues with quality, and inability to meet market demand.

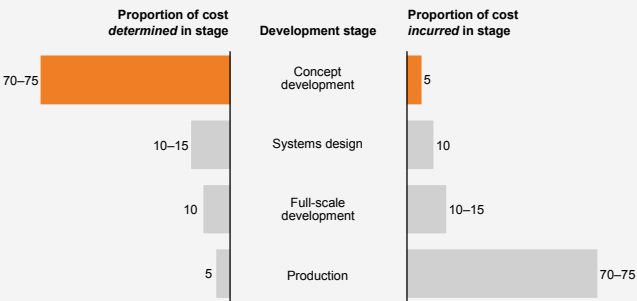
However, changes under way in the regulatory paradigm will open the door to a new and better approach to pharmaceutical technical development. The key elements driving this shift are the regulatory changes enshrined in ICH Q8/9/10 (and soon to be in Q11), the broad push for a quality by design (QbD) approach, and the ever-increasing industry pressure to enhance R&D productivity and manufacturing cost.

Achieving excellence in technical development

We believe that excellence in technical development rests on five key elements: standardized technology platforms, product launch and manufacturing effectiveness, investment optimization, resource utilization, and management of structure and interfaces.

Exhibit 1: Product cost by development phase

Example: Aerospace industry
Percent



Source: Jane’s Defense Weekly; McKinsey analysis

Standardized technology platforms

Almost all major biotech companies, and some major pharma players, have started to standardize their manufacturing platforms. A company following this strategy designs a portfolio of products to be manufactured on the same platform using the same resources: equipment, operations, materials, analytical instruments, and design knowledge. Although different companies are adopting different approaches, all are having a major effect on process capabilities.

Some companies think a standard platform is impossible to achieve or too restrictive to use. Yet once such a platform is in place, developers find they are able to spend their time on the real challenges of a given process rather than on the basics, which are already built into the platform approach.

A platform strategy can make capital and human resources far more efficient. It can reduce the need for manufacturing equipment, sites, and capital pre-investment, allow products to be made at multiple sites or to be switched from one site to another to make best use of capacity, and guide “make versus buy”

decisions. For example, some companies use standard equipment types (such as granulators and tablet presses) across all their development and manufacturing networks for formulation and chemical synthesis. A few go a step further and use the same sites to produce supplies for clinical and commercial launch. When the process and market demand for a given product are stable, its production can be easily transferred to a supply site or vendor. This approach has produced capital savings through the diversification effect as well as savings in engineering, analytical, clinical, and regulatory resources through a reduction in process reengineering.

Where technical resources are concerned, platforming requires less diverse engineering talent, builds deep knowledge of platforms, and allows companies to repeat proven practices easily. Engineering and maintenance are also reduced, boosting capital utilization.

One leading biotech company used technology platforming to develop a robust system that allows it to take an antibody from primary sequence to a clinically suitable production process in four months. The platform includes a practical set of options for media and growth conditions, allowing the company to select parameters that swiftly lead to a stable process. Chromatography media and buffers are highly standardized, as is viral filtration and inactivation. This standardization allows scientists to scan a set of likely conditions quickly and speed up the development of a custom “on-platform” process. The benefits don’t end there: the company also configured its clinical and commercial manufacturing facilities to receive these processes without significant capital expense.

Product launch and manufacturing effectiveness

Decisions on process technology affect a range of factors: development cost, technical skill and personnel requirements for commercial manufacturing, maintenance, and ultimately capital requirements and efficiency. The key drivers for improving process capabilities include the use of design of experiments (DOE) methodology to define process design and the adoption of techniques to establish yield at launch. Companies that adopt these best practices are able to reduce re-filing for small changes in processes. Using a handful of proven practices from outside as well as within the pharmaceutical industry to transform product and process development practices can generate huge benefits in profitability, reliability, and quality.

In addition, the use of DOE and other statistical tools and methods such as PAT, CTQ, and FMEA can significantly reduce quality-related interceptions in processes. Quality can account for up to 25 percent of manufacturing headcount in the pharmaceutical industry, but this can be significantly improved through the application of statistical methods.

Most pharmaceutical companies have made increasing use of quality by design techniques in recent years, although the maturity of implementation varies from company to company. It can be measured in two dimensions: design (methodologies and tools to develop QbD and define the manufacturing control strategy and quality) and operations (leveraging manufacturing capabilities, quality and operating systems, infrastructure, and mindset to capture full value from QbD). Quality by design has already proved its effectiveness in enabling efficient technology transfer, scale-up, and qualification for products making the transition from development to commercial

launch, and consequently many companies are aiming to use QbD processes to develop and launch all their new products.

Although companies have traditionally focused on achieving excellence in their new products, they can make huge strides in their in-line products as well. By using a combination of QbD and lean techniques—chiefly OEE (overall equipment effectiveness) and process-flow improvement—one generics company was able to reduce the unit cost of its best-selling product by some 60 percent. For many years it had used the same process it initially filed, despite the apparent shortcomings of the process and the importance of the product. The company's operations and quality teams had gathered data showing that process, cleaning, and analytical changes would improve manufacturability, but influential gatekeepers considered it taboo to change a filed dossier. To overcome these objections, managers built a comprehensive business case around the bottom-line benefits that the changes would deliver in process cost, time, and quality. Senior corporate leaders recognized the benefits, relaxed internal barriers, and allowed the project to go forward. The filings were approved and the benefits of the new process exceeded expectations.

Investment optimization

Portfolio governance and investment decisions affect the productivity and effectiveness of the technical development organization and the development process overall. Many pharmaceutical companies constantly review investment decisions in commercial process development because of the high costs and uncertainty of success during product launches. While back-loading process development (delaying steps to a later stage) allows

optimal use of resources on high-probability molecules, it can also bring process development onto the critical path of the launch. Cross-functional project teams face a constant tension between the benefits of delaying work (to avoid incurring cost if the program is killed) and accelerating work (to prevent delays, increase efficiency by reducing set-downs, and reduce comparability risk). One good practice in this area is to clarify tradeoffs at the level of both project team and investment governance. Some companies find it useful to develop a menu of investment timing approaches with clearly understood tradeoffs.

Best-practice companies define three or so development pathways as default options, with clear guidelines as to when to front-load, back-load, or take a middle-of-the-road approach, depending on criteria such as the competitive landscape and whether the molecule is a fast follower. This approach makes transparent what is actually critical path and what is not. For example, most “process challenge” activities support regulatory needs and commercial transfer, and can be conducted late in the clinical program. One large company was able to reduce its overall technical development costs by 30 percent with no negative commercial impact by shifting its front-loaded approach to a menu that emphasized back-loading.

Investing in innovative manufacturing process technologies such as cell separation and continuous reactor technology is another way to create competitive advantage. Though such an approach is a hallmark of some industries, such as semi-conductors, it is rare in pharmaceuticals, which faces the challenge of defining a business case on the basis of return on investment under high uncertainty. Front-runner

companies have addressed this challenge by developing a longer-term view on investment that includes a five- to seven-year ROI plan and clearly defined priorities based on business needs such as cost reduction, growth in emerging markets, and long-term network optimization.

Resource utilization

Leading companies have always focused on managing both the capital and operating resources required over a product lifecycle. However, uncertainty over time-to-market and market demand and a lack of clarity over internal resources have contributed to poor outcomes. Leading companies plan realistically and employ flexible facilities whenever possible. They have a better understanding of resource needs, particularly in technical development, which gives management more insight into outliers.

As more companies have started relying on contract research and manufacturing partners, the management of capital efficiency in technical development has become more complex. No longer is it simply about optimizing processes for internal platforms; it is also concerned with developing processes that can be transferred effectively to partners.

Another area that requires attention is developing strategy and processes for clinical manufacturing. Here companies must trade off creating sufficient flexibility to launch out of any site against optimizing utilization at individual plants. For example, one company is able to support all of its clinical needs at a single site even though its pipeline is five times larger than when the site was built.

Good practices in capital management include clarity over resource utilization for both process development and clinical

trial material. Leading companies closely manage a backlog of work (often at about 80 percent asset utilization) but ensure negligible delays in the critical path of important programs. In trials, these companies use more than 70 percent of the supplies they manufacture (with scrap levels of less than 30 percent), as opposed to the 15 percent usage levels that we see at many companies.

Management of structure and interfaces

Technical development demands a close collaboration between R&D and operations that poses challenges for organizational structure. For instance, some aspects of technical development are close to the R&D function, whereas late-stage process development can benefit from close ties with operations. Good practices to encourage effective collaboration across functions include a shared sense of ownership across the project team, equal status for clinical operations and chemistry, manufacturing, and controls (CMC), and seamless transitions within CMC during hand-offs. However, there is no single model that suits all situations; different companies have adopted a variety of approaches ranging from introducing empowered, rigorous project management to aligning incentives across functional leaders to embarking on a complete reorganization.¹



To implement a holistic excellence program in technical development, pharmaceutical companies should establish a transparent business case and long-term roadmap for the program, adopt best practices from other industries such as aerospace and automotive, assess both new and in-line products, develop a strategy that

embraces plants, assets, and quality systems, and align the program with portfolio optimization efforts. By increasing their focus on driving excellence through operational and technological advances, pharmaceutical companies can create significant competitive advantage. They should not let the flap of a butterfly's wings halfway around the world—or in the next-door technical development lab—cause chaos in their operations group. Instead, they should use the power of technical development excellence to build efficiency and effectiveness from the very start.

Note

¹ For more on this topic, see “Quality gates: Raising the standard of pharmaceutical technical development,” *Invention reinvented: McKinsey perspectives on pharmaceutical R&D*, McKinsey & Company, 2010, pp. 40–45.

Ted Fuhr is an associate principal in McKinsey's New Jersey office. **Doane Chilcoat**, **Michele Holcomb**, and **Jatan Shah** are alumni.



What will it take to develop
complex biosimilars?



The coming decade will usher in the second era of product development in the global biosimilar market. Scientific teams seeking to leverage global platforms will need to understand differences in regional requirements, what it will take to satisfy them, and how competitors may respond.

Karsten Dalgaard, Sanjiv Talwar, and John Whang

After nearly three decades of market experience with biotech products, patents on recombinant biologics have started to expire. Off-patent biologics now comprise some 23 percent of a \$100 billion global biologics market enabling a global market for biosimilars worth around \$300 million in 2010. The products approved to date are relatively simple ones based on recombinant versions of endogenous proteins with well-understood structures and pharmacologies. In the EU, for example, 14 biosimilar products have been approved since 2006 under an abbreviated pathway that leverages their similarity to an existing “reference” biologic product.

The coming decade heralds an era of complex biosimilar product development as advanced reference products—largely monoclonal antibodies (mABs) and fusion proteins for the treatment of cancer and autoimmune disease—lose their patent protection. By 2020 over \$100 billion in biologic sales will be off patent. Today, biosimilar versions of important medicines such as Rituxan, Enbrel, Herceptin, Remicade, and Avastin are at various stages of development.

What makes the development of biosimilar mABs more complex than the development of the biosimilar products approved to date is that full physicochemical characterization remains difficult. That is because mABs

are highly complex molecules with secondary and tertiary structures that are subject to post-translational modifications such as glycosylation. They may be heterogeneous and often include subtle variants (“microheterogeneity”) that can result in different potencies and inconsistent efficacy in clinical testing. Even with precise, reliable, and reproducible molecular characterization, it is still possible that a biosimilar mAB might display subtle differences in secondary or tertiary molecular structure from the reference product that cannot be detected by current methods. The regulatory challenge, at least in major markets, is to demonstrate that if such differences exist, they have no impact on the clinical efficacy and safety of a biosimilar mAB relative to its reference.

From a development viewpoint, the winning scientific teams will be those that develop expertise in tackling the following five critical issues:

Designing global development programs

Now that the biosimilar market has expanded to all major countries it is feasible for pharmaceutical companies to design global development programs that take regional guidance into account.

Key definitions

Biologic (recombinant): An original agent usually based on a known human protein, produced through biological processes using recombinant or cloned DNA.

Biosimilars: A biosimilar can be defined as a medicinal product that contains the same active substance as a biological medicine already authorized (its “reference product”). However, the definition and terminology are still evolving and differ from region to region. A biosimilar can be thought of as a non-identical but similar copy of the original. By definition, a biosimilar is not a generic product, since it may show subtle (but not clinically meaningful) differences from the reference product.

Fusion proteins: A single protein comprising a combination of proteins—typically a monoclonal antibody and an immunoglobulin fragment—created using recombinant DNA techniques.

By establishing a common development platform for most markets, companies can minimize the duplication of effort across pre-clinical and clinical development, accelerate development, and reduce investment costs. The conditions needed for such an approach are now in place. Major developed regions such as the EU, US, Japan, and Canada and many of the largest emerging markets such as China, Brazil, South Africa, and India have established biosimilar pathways or produced regulatory guidelines specifically for complex biosimilars. Moreover, in 2010 the WHO offered guidance on biosimilar approval standards for regulatory agencies to use as a basis for local requirements.

The EMA is acknowledged as taking the lead in expanding expected requirements for proof of biosimilar comparability and specifying them for sponsors. In addition to creating a framework for all biosimilars along three dimensions, analytical, pre-clinical, and clinical, it has published class-specific guidelines—for instance, for growth hormone, erythropoietin, and low molecular weight heparins (LMWH)—and guidelines for complex biosimilars (mABs and fusion proteins).

This guidance has informed the biosimilar pathways for other regions, and there are now many commonalities: for example, the interchangeability policy by the State Food and Drug Administration (SFDA) in China matches that of the EMA.

While the FDA is still in the process of defining its guidelines under US healthcare reform law, several scientific elements of EMA guidance can be expected to inform the FDA guidelines. Yet the FDA was the first health authority to establish the scientific underpinnings and concept of comparability for biologics products (based on the 1996 guidance “Demonstration of comparability of human biological products including therapeutic biotechnology-derived products”). One area where the FDA is very different from the EMA is the authority it has to recognize biosimilars as interchangeable in the marketplace on the basis of its scientific concept of comparability.

However, despite the increasing regulatory harmonization across geographies, regional guidance can still vary and pose challenges to common global development programs. An example is how to define

a “global” reference product when labeling differs from country to country. A reference product must be approved by a health authority with a specific label, yet this label often does not match the label approved by another health authority even if the global reference product was manufactured at the same site—in other words, it is the reference label that matters, not what is in the syringe. Future harmonization is likely to consider bridging studies to demonstrate similarity of product, which should eliminate the need to duplicate studies and permit global development platforms to generate usable data for multiple regulatory authorities.

Sometimes the different approaches taken by different regions can have the opposite effect, reducing rather than increasing development requirements and speeding up rather than slowing down development. For example, the FDA recently approved generic enoxaparin without requiring clinical trials, despite the complexity of these molecules. Conventional pharmacokinetic studies are difficult to perform because LMWHs are hard to detect, so absorption and elimination have to be studied by means of pharmacodynamic tests, including the measurement of antifactor Xa and antifactor IIa activity. LMWHs have high heterogeneity, their mode of action is not completely understood, and it is uncertain whether detection markers are appropriate surrogates for clinical outcome. Despite these uncertainties, the FDA relied on scientific criteria other than clinical trials to assess comparability: heparin source material and mode of depolymerization; physicochemical properties; disaccharide building blocks; fragment mapping and sequence of oligosaccharide species; biological and biochemical assays; and in vivo pharmacodynamic profile. This approach, which implies that enoxaparin

is not a biologic, differs markedly from the EMA’s stated requirements for clinical trials.

Given the typically high bar for FDA drug approval, this example suggests there may be potential for shorter development pathways as guidelines and international experience evolve. To enable cost-effective global development, pharmaceutical companies will need to consolidate their efforts to harmonize development requirements, particularly their choice of global reference products and the means by which they define them.

Understanding the tradeoffs in demonstrating similarity

Because mABs and fusion proteins are so complex, they require multiple points of comparison to a reference product to convince regulators of their comparability. For instance, mABs often have large glycosylation chains (quaternary structures) that undergo post-translational modifications and can affect pharmacokinetics, efficacy, and immunogenicity. A comprehensive comparison can address such complexity by using the analytical, pre-clinical, and clinical dimensions laid out by the EMA and used by many other authorities.

The technical challenges in characterizing complex biosimilars, coupled with the fact that variations in manufacturing can significantly alter the tertiary and quaternary product structure, suggest that developers should be thinking in terms of a range of product attributes that confer significant similarity. This understanding should be used to evaluate complex biosimilars for their comparability to reference products bearing in mind structural variations. Sponsors would

need to make compromises in achieving structural similarity along one dimension at the expense of another, and as knowledge of the clinical significance of various structural changes deepens for mABs already on the market, decisions to focus on similarity along certain attributes should become clearer and more easily accepted by health authorities. The creation of structural analytic goalposts or reference points for developing highly similar products will call for tradeoffs and design expertise combined with an understanding of the likely clinical implications.

Developing comprehensive pre-clinical and clinical studies

As a complex biosimilar progresses through comparability stage-gates, both pre-clinical and clinical studies are required to make a full assessment of the similarity of a candidate biosimilar to its reference product. For instance, difficulties arise in using in vivo pharmacokinetic/pharmacodynamic (PK/PD) and toxicological models because complex biosimilars demonstrate species-specific pharmacodynamic profiles that limit the extrapolation of data from one species to another. Indeed, there is no established in vivo pharmacology model other than non-human primates. As a result, extensive in vitro assessments are needed.

Health authorities including the EMA recognize this challenge and have recommended modeling in vivo studies with species used by the original or reference product. Nevertheless, the applicability of non-human primate data to prove comparability in humans may be limited in some cases. Moreover, there is recognition of the ethical constraints of a statistically powered comparative

PD evaluation in non-human primates, which argues for a reliance on in vitro or clinical studies to define PD similarity. In vitro techniques have advanced through techniques such as real-time binding or antigenicity assays, microarray proteomics, and more accurate assessment of binding affinities to targets and Fc receptors, and may offer opportunities to compare the biological responses of originator and biosimilar molecules. PK/PD studies performed in parallel with clinical trials can reduce time to approval while addressing comparability concerns and assessing the wide variability of PK/PD in sub-populations of patients.

Because of the limitations of animal testing, the evaluation of functional similarity will rely to a greater extent on in vitro studies and clinical efficacy. Clinical trials will usually be vital for comparing a complex biosimilar to a reference product, especially given the lack of clear PD indicators for most mABs. Expert planning and input for clinical trial design, including that from relevant health authorities (such as specific scientific advice provided by EMA), will reduce the likelihood of a flawed trial design that may misrepresent the clinical profile of the biosimilar. This is particularly important for biosimilars because of the structural tradeoffs made earlier in development with presumptive clinical implications that health authorities will expect to surface during Phase III studies. Exhibit 1 illustrates a case example of pioneering mAB clinical development under EMA guidance for biosimilar Herceptin.

Common issues to explore on a case-by-case basis include the chosen indication, its equivalence margin, and its extrapolation. The use of surrogate endpoints for complex products will require scientifically robust arguments that justify

Exhibit 1: Empirical clinical trial design

Example: Biosimilar Herceptin, Phase III

	Originator pivotal trial (H0648g)	CT-P06 (Celtrion)*	Comment
Indication	• HER2 over-expressing metastatic breast cancer	• HER2 over-expressing metastatic breast cancer	• Indication extrapolation likely to cover adjuvant breast indications (the largest use) • Gastric CA [†] extrapolation possible given identical dosing
Primary end point	• Time to disease progression	• Objective response rate (ORR) at 6 months, evaluated under RECIST [‡] criteria	• Abbreviation allowed use of ORR as surrogate end point for survival
Secondary end point	• ORR, duration of response, time to treatment failure, overall survival	• Comparable safety and PK bioequivalence	• Combined PK and Phase III trial in sensitive population
Sample size	• 469	• 536 global • 84 Europe	• Largest patient population outside the EU
Key trial results	• Median time to progression: 7.2 for Herceptin, 4.5 for chemotherapy • ORR 50% for Herceptin, 38% for chemotherapy	• Not available	• Efficacy: equivalency would demand 50% ORR with likely 42–58% at 95% CI (confidence intervals) PK: similar half-life of 6 days • Adverse events: ~50% infection rate with non-inferior cardiotoxicity • Immunogenicity: very low or undetectable, as with reference

* Clinical trials focused on EMA requirements and registered in EudraCT database 2009-016197-33; other trials are under way elsewhere [†] Carbohydrate antigen [‡] Response evaluation criteria in solid tumours
Source: EudraCT; McKinsey analysis

the largest margins of benefit can reduce sample size to provide a cheaper and faster market entry point.

Extrapolation from and interchangeability within a primary indication are often determined on a case-by-case basis with input from regulators based on the in-going indication (for instance, rheumatology), requested indication expansion (for instance, oncology or inflammatory bowel disease), and what is understood

regarding the mechanisms of action (MoA) for the various indications. Often multiple MoAs are at play with mABs—for example, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-mediated cytotoxicity, and target binding—and evidence presented in the dossier that is aligned to support one MoA may not support another. Thorough analytical and pre-clinical assessment can pay dividends in providing support for expanded approval. In short, a comprehensive evaluation of candidate biologics may open the door to abbreviated approval pathways.

Focusing on demonstrating long-term immunogenicity and safety

Safety and immunogenicity probably attract more attention than any other aspect of biosimilar development. Serious adverse events with simple biologics, such as pure red cell aplasia from subcutaneous biosimilar erythropoietin (EPO) in patients with chronic kidney disease, has prompted all health authorities in developed markets

adopting this approach in preference to standard efficacy measurements.

The primary indication chosen to be studied in the most sensitive population(s) should provide data to support efficacy not only in the population examined (such as metastatic disease) but also in contiguous populations (such as Stage I or II breast cancer). This has important implications for proving comparable efficacy to the reference product and for developing broad-based indications in a disease area. It is important to remember that populations that help define efficacy may not be ideal for defining safety or immunogenicity; in fact, those patients with co-morbidities that render efficacy analyses more difficult, such as renal disease or heart failure, are often the best for testing margins of safety.

Margins of equivalence drive sample size and consequently have a direct impact on trial costs. Use of the originator pivotal data that provides the margin of benefit over prior standard of care, along with guidance from the authorities, enables the calculation of the sample size needed. Careful selection of an indication with

to raise their level of vigilance. All of them require at least 12 months of safety and immunogenicity data prior to submission, accompanied by 12 to 24 months or more of post-marketing surveillance data. Sponsors' submission plans must include thorough safety data captured during pivotal study execution, as well as proposed programs for pharmacovigilance. It is vital that companies manage safety and immunogenicity as seriously as the authorities do.

To meet this high bar, sponsors should assess the capabilities of their regulatory and safety programs. High-performing programs not only detect adverse events during clinical trials and after marketing approval, but also send a clear signal to authorities that their concerns over potential harm are shared—for example, by including a pre-launch definition in the dossier of post-launch surveillance studies. Beyond that, investing in pharmacovigilance and safety supports claims of quality, good manufacturing and clinical practices, purity, and so on, providing proof that the product is considered a genuine candidate for wide use. Traceability, anti-drug antibody tests, and continuously updated adverse event rates for practitioners to see are some of the capabilities that sponsors should demonstrate to authorities as part of the dossier so as to generate confidence in the submission. Scientific teams will need to provide strong long-term immunogenicity safeguards through post-marketing surveillance systems, focus on the traceability of adverse events, and supply clinical information and potentially diagnostic immunogenicity support for provider adoption.

Although the set of complex biologics that are expected to lose patent protection this decade is limited, it

includes blockbusters such as Enbrel, Herceptin, Remicade, Rituxan, Erbitux, Humira, Avastin, and Vectibix. In terms of strategic development, Herceptin may offer the simplest case among these: it is essentially a single broad indication and gold standard first-line adjuvant and metastatic breast cancer treatment preferred when possible notwithstanding a gastric cancer indication. Others in the list present greater development challenges or will at least require careful strategic choices of indication and its extrapolation feasibility based on a scientific rationale. For example, Remicade has six major non-pediatric indications in developed markets and Enbrel has five (although the MoAs may be closely linked). Rituxan, while among the most widely developed biosimilars, has one of the broadest indication sets among the complex biologics, spanning autoimmune and oncology conditions that are each likely to require separate development. Where there are no appropriate PD markers and the clinical response can be highly variable, as with Avastin, a biologic license application (BLA) may allow for more abbreviated development. In such cases, it is critical to have an expert regulatory function working closely with authorities as guidelines continue to be shaped.

Developing a deep understanding of possible competitive responses

To inform their business cases and portfolio decisions for biosimilars, scientific teams will need to develop a deep understanding of how originators may respond. Branded pharma employs several common lines of defense against biosimilars, such as:

- **The development of next-generation biobetters:** for instance, trastuzumab-DM1 (T-DM1) for Herceptin. The results of this strategy have been mixed, and evidence suggests that developing biobetters may be as risky as developing innovative antibodies. A deep understanding of an originator's biobetter approach can help sponsors define what tradeoffs should be made in pre-clinical development, with implications for Phase III design.
- **The promotion of innovative new molecules with entirely new mechanisms of action:** for instance, Pertuzumab in combination with Herceptin. New oral small molecules could represent a threat to mABs, especially for autoimmune diseases: an example is Tofacitinib for rheumatoid arthritis. These game-changing molecules have implications for the future standard of care in developed regions but leave developing regions still in play for biosimilars currently in development.
- **Lifecycle strategies such as subcutaneous formulations for existing brands:** for instance, Halozyme is applying its proprietary Enhance technology to develop subcutaneous formulation of Herceptin which may drive adoption of the branded product in some markets.
- **Clinical trials exploring shorter duration of branded biologics:** for instance, shorter-duration Herceptin trials are currently under way in multiple countries. If successful, they would likely mitigate the risk of adverse cardiac events. As more information is acquired regarding originator

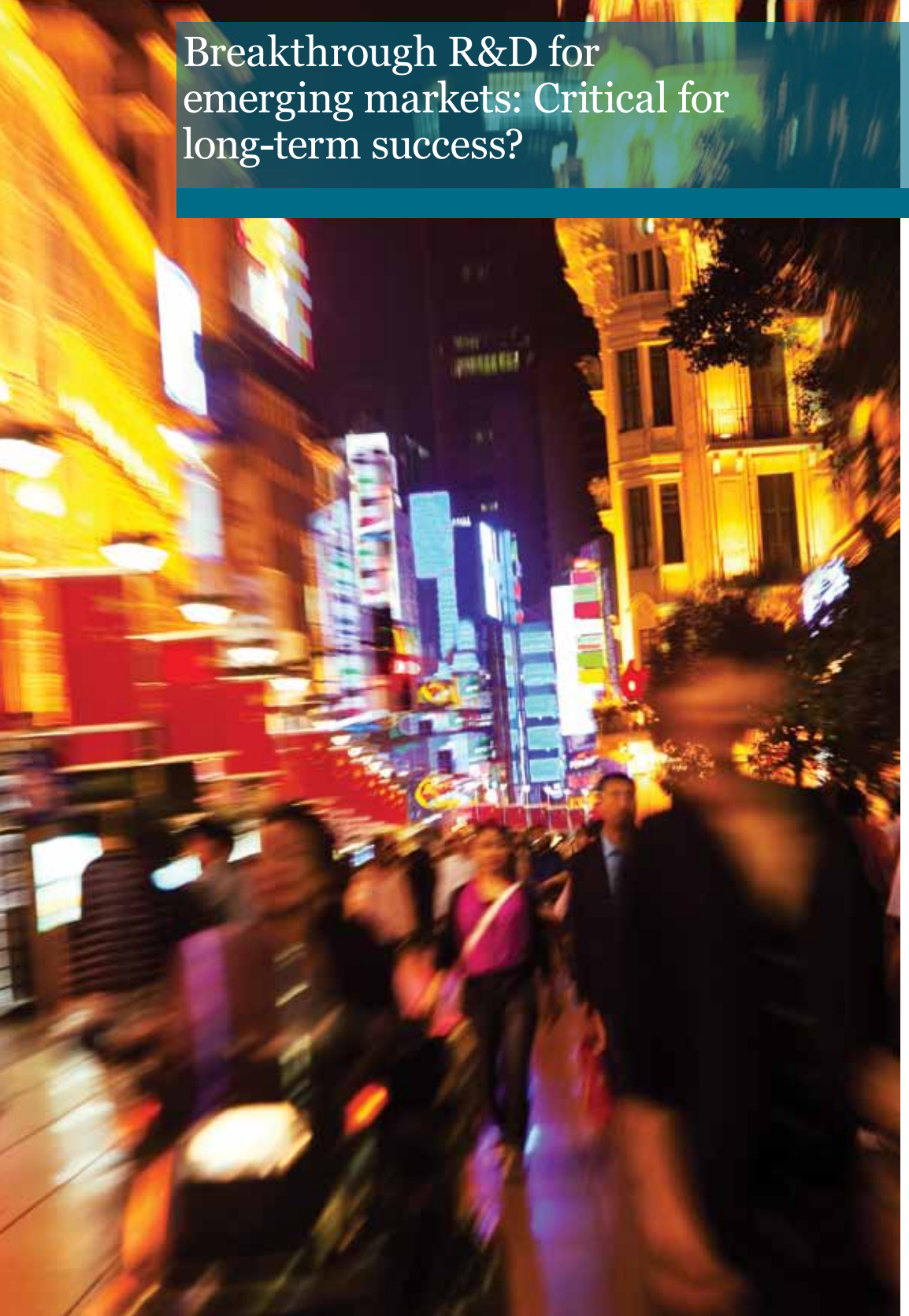
products, the design of Phase III studies can be modified to incorporate clinical experience so as to increase the likelihood of a successful outcome and reduce the rate of adverse events.

- **Patent ring fences.** Key patents vary significantly by country, and data exclusivity can sometimes even vary by indication. Some patents can represent development challenges: for example, Enbrel's aqueous formulation, which is vital to preserving molecular structure, may enjoy patent protection beyond 2020 in the US. Biosimilar teams may have to develop lyophilized versions, which can be technically difficult, or find ways to formulate their own aqueous versions.



Over the next decade the biosimilar market will be transformed by complex biosimilars, the largest opportunity. As pathways are introduced across the globe for complex biosimilars, the challenges associated with each development decision will be compounded. Early entrants will have the advantage, but scientific teams seeking to leverage a global platform must be equipped with an understanding of key regional similarities and differences in requirements, the scope and capabilities needed to meet those requirements, and the likely responses from competitors in the market. Teams that can rationalize development investments against the commercial case along the five key considerations we have outlined here will be best positioned to navigate the evolving biosimilar opportunity.

Breakthrough R&D for emerging markets: Critical for long-term success?



Pharma companies pursuing growth in emerging markets will increasingly need to adapt their portfolio to address local requirements. The right R&D strategy will involve reducing costs so that they can develop innovative drugs tailored to emerging market needs and still make a profit.

Sanjiv Talwar, Shail Thaker, and Matthew Wilson

With cost pressures in established pharmaceutical markets set to continue into the foreseeable future, emerging markets will soon start to contribute the largest share of industry growth. This rising share is driven by a large and growing unmet medical need and by an improvement in these markets' ability to pay for drugs that is driven by increasing affluence among patients and expanding and deepening government coverage. As a result, many leading pharma companies have committed to ambitious growth plans for these markets and are placing material investments to back them up. However, the success formula for these markets has yet to be firmly established and we believe that a new approach to R&D will be a critical component.

Approaching the tipping point?

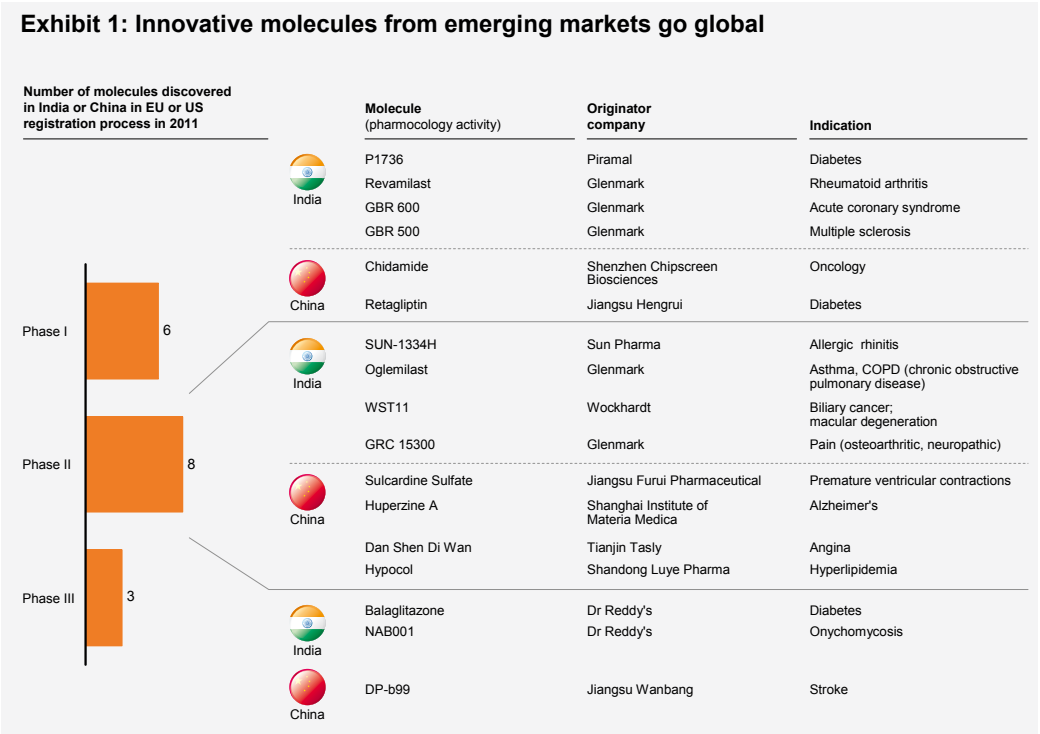
In the past, multinational corporations (MNCs) have approached emerging markets as an opportunity to capture additional revenue for existing products rather than as a diverse set of markets with unique needs of their own. Even when successful innovative products have been created for local markets, they have come about either through leveraging existing breakthroughs (for example, when the understanding in traditional Chinese

medicine of the herb artemisinin was exploited by Coartem to treat malaria) or by necessity (as with the identification of ethnic sub-populations where drugs are effective, for instance in the case of Iressa).

In the past five years, pharma companies have received a great deal of publicity for their investments in R&D sites and partnerships in emerging markets. As an example, more than 20 sites have been built by global pharma companies in China,¹ and some emerging markets have seen rapid growth of up to 30 percent per year (compared with 7 percent in the US) in the number of clinical trials initiated.² However, these investments have generally been focused on supporting the global portfolio by sourcing services and patients for trials at low cost, or developing capabilities in incremental product innovation such as fixed-dose combinations.

This approach is implicitly underpinned by the belief that developing innovative products specifically for emerging markets does not make economic sense. However, several factors are now challenging this viewpoint:

There is evidence that tapping unmet needs provides a credible revenue opportunity. Local companies in India, China, and Korea have had success



in developing products to meet local needs. They go beyond duplicating or reformulating global drugs and develop genuinely innovative drugs. Examples include Simcere's innovative cancer drug Endu in China, Hanmi's novel combination Amosartan in Korea, and CP Guojian's pipeline of innovative monoclonal antibodies, again in China.

Local R&D capabilities are improving. Academic, government, and private sector investments into life science research are beginning to pay off. If we take publication as a measure, China now ranks fourth in the world for medical publications in general³ and is not far behind Japan for publication in top journals.⁴ Other countries are not far behind, with average citations for papers produced in South Korea, Singapore, and Russia running at levels comparable to those of many western European nations.⁵

Early evidence of the quality of local work can be seen in the innovative products developed in emerging markets that are beginning to reach global markets. As Exhibit 1 indicates, there are at least 11 such drugs from China and India alone in Phase II and III at the moment.

Another indication of improving local capabilities is the growing number of new partnerships in which multinationals seek out innovation from local emerging market players. Examples involving Indian companies include Sanofi's deal with Glenmark on an immunology monoclonal antibody, Pfizer's pact with Biocon for its insulin portfolio, and Merck's joint venture with Sun Pharma for innovative formulations. The alliance between Roche and Russia's TeaRx for the development of Factor Xa inhibitors is another example of a global company pursuing innovation with the help of a local partner.

Local R&D can help to secure access to some key growth markets. Governments are increasingly rewarding local R&D efforts that go beyond including local patients in global clinical trials. Many countries have identified the development of local pharma R&D as a strategic priority and are aligning their policies to support it.

As an example, the Russian government has outlined a strategy for long-term innovation as part of its Pharma 2020 vision. Its aspiration is to replace 50 percent of imported innovative branded drugs (that is, those other than generics and branded generics) with locally developed ones. This strategy, like Russia's local manufacturing policy, is likely to be underpinned by legislative and regulatory mechanisms

In response to such initiatives, MNCs are showing early signs of movement to develop innovative products specific to emerging markets. For instance, Lilly's new R&D center in China focuses on developing diabetes products exclusively

for the local market. However, such efforts are still in their infancy and do not represent a general trend as of yet.

Where is the real opportunity for innovative R&D?

As emerging markets develop and start to share common health challenges with developed markets, we can expect to see a broad convergence in epidemiology, particularly in chronic diseases such as cardiovascular and metabolic diseases. Consequently, many emerging market needs can be met by means of R&D focused on developed markets, as the historic global success of many major drugs from the US and Europe would suggest.

However, there are unique opportunities specific to emerging markets that exist alongside these shared needs. We have identified five types for multinationals to consider, as itemized in Exhibit 2. All could

Exhibit 2: Attractive areas in emerging markets for innovative R&D			
	Area	Examples of therapeutic areas and products	Considerations for multinationals
Diseases specific to emerging markets	1 Previously neglected widespread diseases that may become commercially viable	<ul style="list-style-type: none">MalariaTuberculosisZoonotic diseases (e.g., Chagas disease, Dengue)	<ul style="list-style-type: none">Emerging mechanisms to foster additional R&D (e.g., product development partnerships)Molecular genomic approaches (e.g., for malaria, zoonosis) to reduce discovery and development costsDrug resistance patterns
	2 Genotype-specific diseases	<ul style="list-style-type: none">HCC (hepatocellular carcinoma)Myopic CNV (choroidal neovascularization)	<ul style="list-style-type: none">May be able to access government funding to reduce costsInnovation approaches could filter to developed regions
Global diseases with local nuances	3 Opportunities created by differences in local standard of care or epidemiology	<ul style="list-style-type: none">Diabetes	<ul style="list-style-type: none">May involve research in different areas (e.g., gene polymorphism in diabetes)Alternative target product profiles may be needed to meet local prescribing preferences
	4 Diseases with high incidence in emerging markets but low priority at global level	<ul style="list-style-type: none">COPD (chronic obstructive pulmonary disease)HPV (human papillomavirus)Hepatitis	<ul style="list-style-type: none">Must be well recognized by payors or prescribers (e.g., depression has high incidence in emerging markets but is often not diagnosed or treated)
	5 Differences in consumer preferences	<ul style="list-style-type: none">FDCs (fixed-dose combinations)DevicesHeat-stable formulationsCheaper versions	<ul style="list-style-type: none">Substantial variations from country to countryMay require more than simple bioequivalenceMay include branded generics, generics, biosimilars, biobetters

address substantial unmet needs and all have the potential to generate material revenues, though these might be at different margin levels from those currently enjoyed by the industry. However, traditional R&D approaches have yet to target or capitalize on these areas in any significant way.

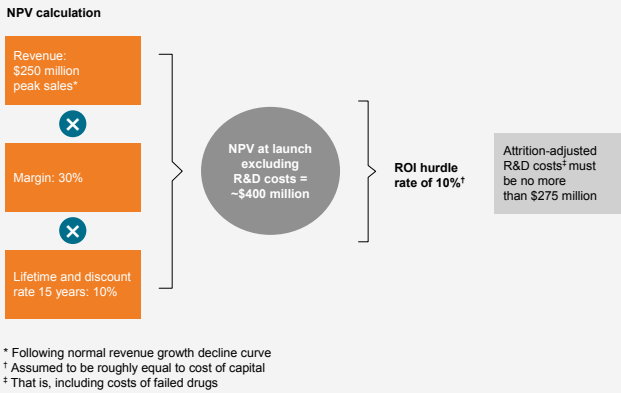
So what's stopping the industry? The most common objection we hear is “Emerging market opportunities are too small—the numbers won’t add up.” No doubt scale does pose a challenge. Peak potential revenues of a successful product in emerging markets are in the region of \$300 to \$500 million, with lower margins than in established markets. However, the longer product lifecycles and significant growth in these markets have a positive impact on the calculation of the drug’s net present value (NPV).

If we make a conservative set of basic assumptions about the development costs of a drug focused on key emerging markets and factor in attrition, the implication is that an MNC will need to be able to develop such a product for no more than \$275 million. Exhibit 3 lays out the calculation for an illustrative product under these assumptions.

The analysis does not take into account the possible benefits of conducting targeted R&D in terms of improved access to the market concerned. Such benefits are difficult to quantify, but could be material. Even without them, we believe that pharma companies could deliver profitable products if they were willing to modify their classic developed-world R&D approach.

Exhibit 3: Conservative calculation of R&D cost threshold

Illustration using standard assumptions, with adjustment for attrition



What do MNCs need to do differently?

To capture the opportunity, global pharma companies would need to do three things: choose the right opportunities, change their approach to R&D, and adjust their NPV equations.

Choose the right opportunities

We see five broad areas of opportunity, as laid out in Exhibit 2. The relative weighting of these opportunities differs by country, depending on local needs. To find the right targets, an MNC will require deep local knowledge about both the nature of these needs and the willingness of payors to support them. This in turn will typically require its R&D organization to form partnerships with high-performing local medical and market access functions.

Change the R&D approach

Applying a traditional approach to the development of a drug for emerging markets would incur high costs that would exceed the drug’s projected net present value on an attrition-adjusted basis. However, focusing exclusively on emerging markets allows companies to:

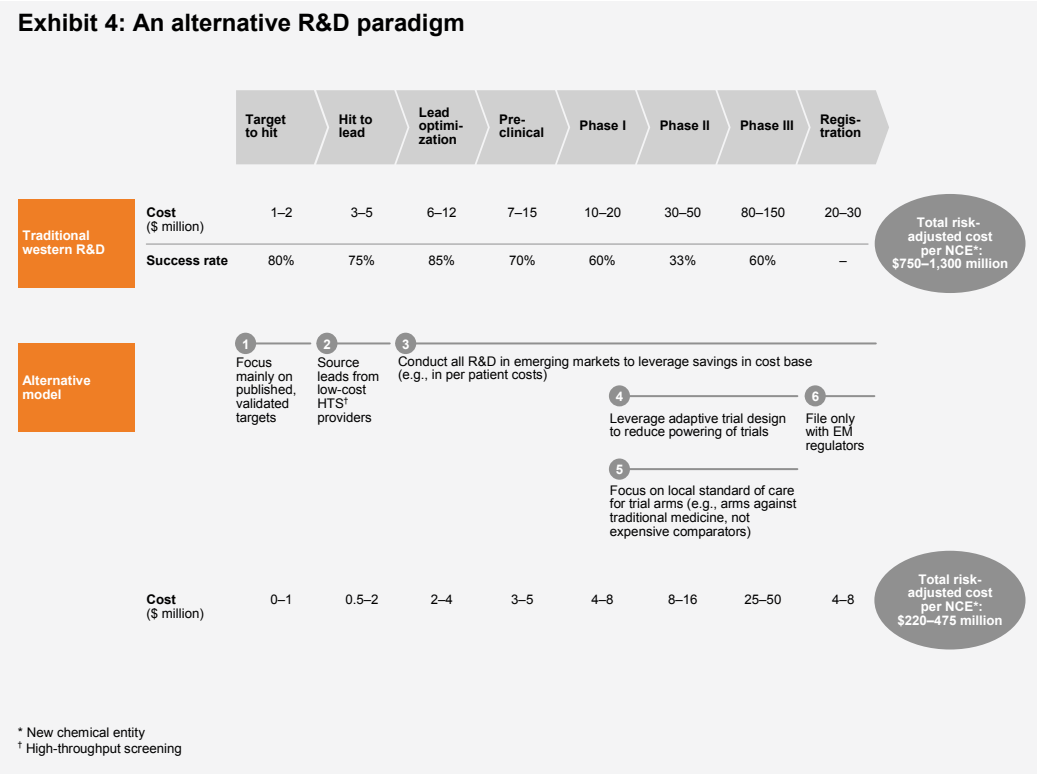
Explore new drug development paradigms. Leveraging adaptive trial design to reduce the powering of trials and rethinking trial arms (for instance, by conducting arms against traditional medicines rather than more costly conventional drugs) offer opportunities to depart from the traditional drug development approach.

Take advantage of low-cost local R&D capabilities. Conducting all aspects of the R&D process in emerging markets—for instance, using local patients only, rather than those from Europe or the US—and taking advantage of lower labor and per patient costs will help save money across the entire value chain. Factoring in lower costs for internal clinicians and forming partnerships with large hospitals to recruit patients rapidly and at lower cost per patient would enable a Phase II trial to be

run for \$8 to \$16 million as opposed to the usual \$30 to \$50 million in developed markets. Interviews with local companies in India and elsewhere suggest that they may be able to shave even more off this cost.

Target filing with regulators in emerging markets only. In the past, regulators in emerging markets have been unlikely to approve products from multinationals that target only emerging markets. However, the SFDA (State Food & Drug Administration in China) and DCGI (Drugs Controller General of India) have shown increasing willingness to make independent approvals, and pathways such as EMA Article 58 and WHO prequalification offer potentially cheaper and faster alternatives to a traditional FDA or EMA filing.

As Exhibit 4 illustrates, rough estimates indicate how these approaches could



cut risk-adjusted R&D costs from traditional levels of \$750 million to \$1.3 billion down to as little as \$220 to \$475 million, assuming attrition rates that are comparable with those in traditional drug development. That means that MNCs may be able to meet the required cost hurdle for profitable drug development purely by changing their R&D approach.

Moreover, the cost could come down even further if attrition proves not to be as high as it is in traditional areas (for instance, if there are fewer failures due to lack of differentiation since the standard of care is limited) or if novel techniques like adaptive trial design are fully applied.

Adjust the NPV equation

To shift the economics in their favor, companies can seek out new sources of funding, capitalize on low-cost manufacturing, and pursue alternative commercial models.

Seek out new sources of funding.

Substantial pools of government and other institutional funding have emerged that companies could access to conduct R&D in emerging markets. Governments increasingly view R&D as a core capability that they want to have in their country, and they are offering a variety of incentives. Funding opportunities include:

- Brazil: billions of dollars of funding in FINEP, FAPESP, and other institutes, as well as tax breaks of 160 to 180 percent
- Russia: funding and preferential access in exchange for local investments at Skolkovo, the R&D “city” near Moscow
- China: local R&D capability development given priority and funding in the twelfth five-year plan (at least \$6 billion committed to local R&D up to 2015), as well as through national biotech zones

- Malaysia: healthcare industry development agency with standing budget for co-investments.

In addition, foundations and product development partnerships are taking more and more interest in investing in emerging markets, particularly in the area of neglected diseases.

Capitalize on low-cost manufacturing to support margins.

There are multiple business models that can be adopted to reduce capital and operating expenditure while still maintaining MNC standards for quality and compliance in active pharmaceutical ingredient (API), formulation, and packaging. Options range from captive manufacturing plants (like those of Sanofi-Aventis in India) to tactical short-term one-off contract manufacturing deals (like that of Jubilant and GlaxoSmithKline). There is some variation from region to region, but opportunities for cost savings go beyond lower manufacturing labor costs to include improvements in cost of goods sold through a reduction in overhead and capital costs, lower API sourcing cost, and other benefits such as tax shields.

Integrate alternative commercial

models. The rapidly evolving commercial landscape in emerging markets presents incremental opportunities to broaden the revenue base via options such as new distribution models, a multi-channel approach for the emerging middle class, and partnerships for joint promotion or marketing. There is also an opportunity to broaden the accessible patient base by developing effective pricing approaches.



Success in emerging markets is a strategic pillar for many pharma companies, but the increasing complexity of these markets means that players are likely to need a portfolio of mutually reinforcing initiatives in order to achieve it. The approach outlined above could be a powerful ingredient in this mix, and a useful complement to the portfolio expansion and branded generic deals we see today. Companies that aspire to long-term leadership in emerging markets need to invest considerable effort to get this approach right. However, the winners could reap considerable rewards in the form of a high-growth emerging markets portfolio and a major boost in the value of their global portfolio in these markets as well.

Notes

- 1 For more on China, see “Debunking the myths about R&D talent in China,” pp. 96–105.
- 2 “Clinical trials submitted in marketing authorization applications to the EMA,” EMA, November 2010.
- 3 SCImago Journal & Country Rank, October 2010.
- 4 PubMed; the top journals are *Science*, *Nature*, *Cell*, *New England Journal of Medicine*, and *PNAS*.
- 5 Robert D. Atkinson and Scott M. Andes, “The Atlantic century: Benchmarking EU and US innovation and competitiveness,” Information Technology & Innovation Foundation, February 2009.

Sanjiv Talwar is a consultant in McKinsey’s New Jersey office, **Shail Thaker** is a principal in the London office, and **Matthew Wilson** is an associate principal in the New York office. The authors would like to thank Ajay Dhankhar, Matthias Evers, Sumin Koo, Martin Møller, Charles Sekwalor, and Navjot Singh for their contributions.

The background of the page is an abstract composition. It features large, bold, red shapes on a yellow background. On the left, there is a large, curved red shape. On the right, there is a vertical red bar. In the lower center, there is a red ampersand (&). At the top, there are black, irregular shapes that look like footprints or abstract forms. A teal-colored horizontal band is positioned across the upper part of the page, containing the title text.

R&D strategies in emerging economies: Findings from a McKinsey cross- industry survey

Two-thirds of executives from a range of industries say their companies conduct R&D in emerging markets, but less than a fifth develop products specifically for these markets. Executives also report that underdeveloped management skills and a lack of knowledge sharing remain challenging.

Economies such as China, India, and Brazil are emerging from the global recession with high expectations for growth. This presents global companies with new markets, access to lower operating costs, and unprecedented opportunities to broaden their research and development efforts in the coming years. Yet in McKinsey's third annual survey on R&D across industries,¹ fully one-third of executives around the world say their companies are not doing any R&D work in emerging economies.² However, every respondent from the companies we identified as "high-performing innovators"³ says that his or her organization conducts R&D in emerging economies.

Of the two-thirds of respondents whose companies do pursue such efforts, most say that their R&D is focused on either global product platforms or local innovation in emerging economies; R&D for developed markets only is not a major focus. The bulk of overall development spending—59 percent—remains in-house. Companies that focus on local innovation in emerging economies spend significantly more of their in-house R&D budgets in those economies, whereas companies focusing on global product platforms spend more of their in-house budget in developed economies.

The reasons given for pursuing emerging-economy R&D depend

on the companies' goals. Among respondents who say their companies focus on R&D for global platforms, 44 percent cite lower costs as the reason; among those pursuing innovation for emerging markets, 39 percent cite access to customer insights.

Forty percent of respondents say their companies adjust product features to meet the needs of emerging-market consumers, while just 16 percent say their companies develop entirely new products for these customers (Exhibit 1).

The R&D destinations most commonly reported by respondents are China and India among countries and Shanghai and Beijing among cities. However, there is no single dominant destination: indeed, a quarter of executives say their companies put R&D resources in locations outside the ten leading destinations that our survey asked about.⁴

The dominant approach to talent management in emerging-economy R&D is retention (cited by 37 percent of respondents), followed by aggressive hiring from top sources such as competitors, universities, or other industries (26 percent). Many respondents feel that R&D managers in emerging economies lag behind their developed-world peers in terms of leadership, communication, and management skills, although they

have the edge where local knowledge and understanding of their business environment are concerned.

Executives were also in broad agreement that their companies struggle to share knowledge effectively: 64 percent say their companies are no better than “somewhat effective” at it. Collaboration is still largely conducted through long-established means such as telephone and video conferences and face-to-face meetings, although high-performing innovators are more likely to use central knowledge databases and global communities of practice as additional means of sharing information. Moreover, most decisions about R&D are made centrally: 72 percent of respondents say that decisions on criteria for evaluating project portfolios are made by central rather than local offices, for instance. Still, companies do defer to local centers in some circumstances: 49 percent of respondents say that decisions about choosing local partnerships are made locally, whereas 45 percent say they are made centrally.

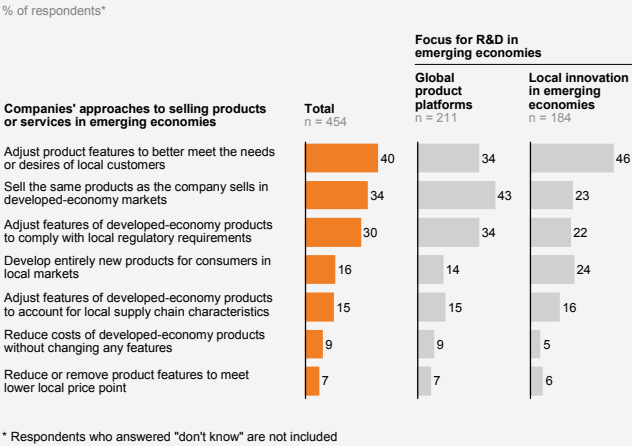
Notes

- 1 The online survey was in the field from March 1 to March 11, 2011, and received responses from 1,173 executives representing the full range of regions, industries, functional specialties, tenures, and company sizes.
- 2 We define “emerging economies” as countries and regions experiencing rapid growth and industrialization. They include countries such as China and India, subregions within those countries such as Shanghai Municipality, and countries in regions such as Latin America, eastern Europe, and southeast Asia.
- 3 These are companies that, according to respondents, have had higher rates of organic growth than competitors and realized more than 30 percent of that growth through new products developed in-house.
- 4 The destinations we selected for the survey were those ranked among the top ten in both average R&D investment levels over the period 2006–10 and higher than average recent growth in R&D investment (determined by comparing growth in 2009–10 with the average for 2003–10).

This is adapted from an article that first appeared in *McKinsey Quarterly* in April 2011 and subsequently in *Research-Technology Management* in July–August 2011.

The contributors to the development and analysis of the survey include **Christie Barrett**, a consultant in McKinsey’s Detroit office; **Peet van Biljon**, a consultant in the Washington, DC office; and **Chris Musso**, a principal in the Cleveland office.

Exhibit 1: R&D focus shapes the work approach



For companies contemplating a more global R&D footprint, the perceived differences in skills between R&D managers in emerging and developed economies should underscore the importance of paying attention to talent and organizational development as well as operational best practices during expansion. In our experience, the best innovators in emerging economies excel at both.



Can innovation hubs help cure the ills of pharmaceutical R&D?



Companies grappling with rising R&D costs and uncertain results are looking to source innovation externally, but that isn't their only option. By organizing around innovation hubs—and perhaps even helping to develop new ones—they can improve their access to creativity, talent, and influence.

Chris Llewellyn, Dmitry Podpolny, and Tamara Rajah

Over the past hundred years the pharmaceutical industry has improved the quality of life of patients around the world by bringing innovative products to market. However, the engine of its success is starting to falter as R&D becomes increasingly costly and difficult to maintain. As a result, pharmaceutical companies are looking to source innovation outside their organizations, but the limited opportunities available, coupled with the rising costs, mean that this solution does not fit all cases.

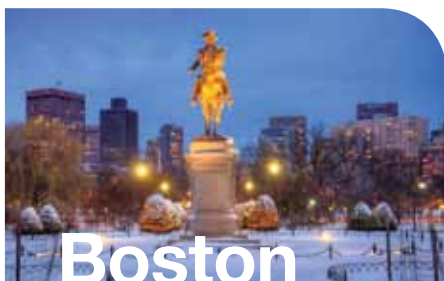
There is another option, though. Local innovation hubs have been recognized for years as sites of economic, scientific, and technological advances. Indeed, pharmaceutical companies have been using established hubs to drive a large part of their R&D for some time, and have located their sites accordingly. But if companies want to access and nurture innovation in the medium and long term, we believe they should renew their focus on hubs and on ways of extracting value from them.

What are innovation hubs?

An innovation hub brings together academic institutions, small and medium-sized enterprises (SMEs), large

corporations, and investors in close proximity. Having so much variety at one location enables productive networks to form, drives the development of local infrastructure, and helps to establish a prime operating environment that becomes a prominent destination for talent and investment and fuels the creation and growth of new ideas. Innovation hubs are a well-known feature of the economic landscape and the subject of many studies. Michael Porter, Daniel Isenberg, and others have described their role in generating competitive advantages for participants and wider benefits for the economy as a whole, such as economic growth, greater life expectancy for SMEs, and the creation of new spin-off businesses.¹ As the economy and the life science industry evolve, governments, academic institutions, investors, and pharmaceutical multinationals are showing an increasing interest in the development of these hubs.

Several successful innovation hubs already exist in life science R&D, such as those in Boston (see panel), San Francisco, and New Jersey in the US, in Switzerland, and in Cambridge in the UK. They represent epicenters of global pharmaceutical R&D, and account for up to 70 percent of all existing R&D pipelines. They typically emerge around large universities or medical centers that are prominent in life sciences research.



- Most top pharma companies present, including Pfizer, Merck, Novartis, Sanofi, GSK, AstraZeneca, BMS, Boehringer Ingelheim, and Amgen
- 480 biotechs
- Harvard (Cambridge) and MIT
- Massachusetts General Hospital, Brigham & Women's, Dana-Farber Cancer Institute, and Beth Israel Deaconess Medical Center
- Big players in life science such as Pfizer, Sanofi, Novartis, and Amgen have increased their R&D operations in Boston
- Collaborations between pharma and academia include Pfizer to invest \$100 million in a network of research partnerships with eight of Boston's leading biomedical research centers and a thriving alliance since 2005 between Novartis and Dana-Farber Cancer Institute
- 600 new life science PhDs in Massachusetts every year
- Almost 900 drugs in development
- \$1.6 billion in NIH funding in 2008 (7.8% of total NIH funding)
- New England region had \$1.2 billion in seed and early-stage funding for biotechnology in 2009–2010
- 124 startup biotechs in New England in 2009–2010
- Pharma/biotechnology cluster with corporate R&D spend of \$6.5 billion and employment in excess of 59,000
- Investment tax credit, economic development incentives, R&D tax credit
- Low-interest loans from Citizens Bank and state of Massachusetts

Most develop naturally from an emerging local culture of new enterprise. Others (like Singapore) have their origins in government support or through pharmaceutical companies acting as anchor tenants (as in the Medicon Valley biotech cluster spanning Denmark and Sweden).

Competition for talent and ideas intensifies in the most successful hubs, and pharmaceutical companies gravitate toward them to reap the benefits. For example, almost all of the top 10 pharma companies have R&D sites in the Boston area. New hubs are continuing to emerge, such as those in Singapore and Shanghai (see panel). Seven large pharma companies have opened R&D facilities in China in the past six years alone, but they are still struggling to create the ecosystems they need to sustain innovation activities.

Taking a more active role in hubs

Governments in the UK, China, Singapore, Israel, and around the world are increasingly identifying life science as the industry of the future, and are exploring ways to stimulate the emergence of hubs within their borders as an element of their economic growth strategy. The challenge they face is in defining the precise role they wish to play. Although they have succeeded as initiators and convenors in several countries, such as Singapore and Israel, they do not necessarily excel at defining the strategic focus of a hub or starting up a new one from scratch.

For their part, pharmaceutical companies typically take a reactive approach, going where proven innovation leads them. Although driving hubs seems to be in their best interests collectively, that does not seem to be true for any single company in particular: a case of the “tragedy of



- Home to more than 200 biopharmaceutical enterprises such as Roche, GSK, Sankyo, Lilly, and Tsumura
- More than 30 national research and development institutions
- Shanghai Institutes for Biological Sciences (SIBS) employs over 1,200 scientists and has around 1,400 postgraduate students. It comprises eight former research institutes and a multi-disciplinary research center
- Office of Technology Transfer set up to perform invention evaluation, IP protection, licencing, and incubator management

the commons,” where no player is willing to invest significant resources to create benefits that will accrue to all. However, we believe that companies should take a more active role and seize opportunities created by governments and other institutions that have recently started focusing on innovation (particularly in the life sciences space) as a driver of economic growth.

We see scope for a single company to lead the charge in a particular country by striving to develop a common agenda with government and other stakeholders to drive innovation in a particular location. That company should also explore shared interests so as to engage other pharmaceutical companies and increase collaboration in the pre-competitive space. For instance, it could pursue opportunities for open innovation in

traditional therapeutic or disease areas and seek alternate competitive sources of IP, perhaps in the commercialization stages.

Governments would continue to play an important role, acting as convenors and collaborating closely with—or perhaps taking their direction from—a particular pharmaceutical company or group of companies that engages early in the process and shapes the way the hub develops. In some cases, especially in emerging markets, companies could take the lead by acting as convenors themselves in collaboration with government or other companies.

The benefits of closer involvement

The returns from concentrated involvement in the shaping of an innovation hub could be significant. They include:

Access to innovation. Maximizing privileged and sustainable access to innovation becomes even more important as R&D organizations seek to externalize innovation to reduce risk and variabilize their cost base.

The ability to target innovation to specific areas. Leading the development of a hub could help companies to direct innovation toward particular disease areas or new technologies and capabilities. Concentrated efforts are already being made in the areas of predictive science, genomics, and stem cells. Collaborating in a hub may also put companies in a position to stimulate the market through initiatives like the X Prize.

An opportunity to shape policy. As payors and regulators develop their long-

term healthcare strategies, pharmaceutical companies that actively participate in hubs may be able to gain access to the discussions that influence policy making. This is particularly important in emerging markets, where policy makers are keen to engage with and learn from sophisticated stakeholders. Companies that take part in this process will be better placed to petition the government for regulatory changes to support innovation, whether they be reforms in tax, IP, or clinical trials.

Access to talent. Taking part in hubs can improve a pharmaceutical company’s access to world-class R&D talent through the network of apprenticeships that grow up within the hub and through the proximity of academic institutions that provide a ready source of talent.

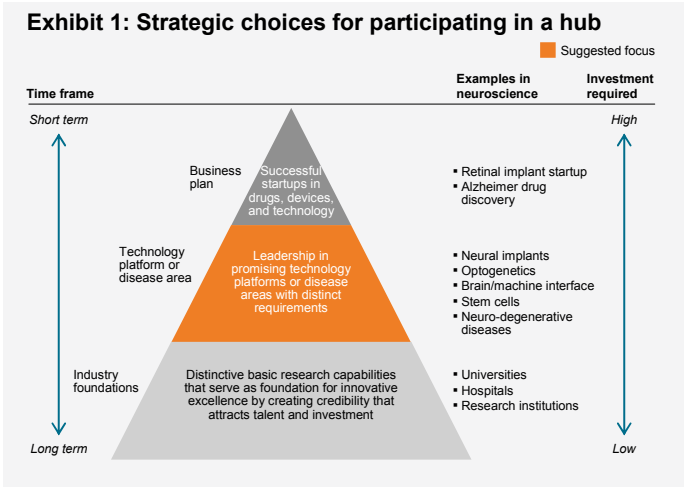
Optimizing their geographic footprint. As companies consolidate their geographic R&D presence, participating in hubs can give them security about their long-term locations, as well as the benefits of dedicated investment in infrastructure and promotion by other hub members.

Key success factors

Pharmaceutical companies thinking about investing in innovation hubs should pay attention to a few important factors:

Strategic focus

One approach is that of “let a thousand flowers bloom,” where there is no single strategic focus and the development of the



hub rests on efforts such as supporting the education system to develop talent, ensuring availability of angel and venture capital funding, and providing tax incentives for entrepreneurs or large multinational companies to set up their operations in a particular location. This approach has led to the evolution of hubs in Boston, Singapore, and North Carolina, among others. It is a long-term play, but we believe it is not enough to differentiate one region from another, and whether it succeeds is likely to depend on serendipity.

At the other end of the spectrum, some hubs have focused on a specific business idea that if well chosen can create value quickly (as with the South Korean government’s focus on chips). However, the narrow focus carries a lot of risk and is less likely to lead to a sustainable development.

The appropriate focus in our view is a technological platform with multiple applications in which the region already has a natural competitive advantage (Exhibit 1). Such an advantage can arise either from the demand side (for instance, through heavy government-led market demand, as with the defense industry

in Israel), or from the supply side (the availability of a distinctive technology or talent such as advanced manufacturing capabilities or a pool of highly qualified technicians). This focus should then shape the foundations for the hub—incentive programs, talent management, pump priming, and so on—along with the setting of clear objectives and expectations.

Stakeholders

A hub’s distinctiveness and sustainability will rely on coexistence between companies (large and small, new and established, foreign and local, headquarters and satellites), academic institutions with a track record of world-leading life science research, and local angels and venture capital firms willing to invest in innovation in this field. A convenor must be in place to bring these stakeholders together: a hub can succeed only if all stakeholder groups are aligned on a strategic focus. Governments have traditionally played the convenor role, and are often seen as initiators of hubs for that reason.

Ecosystem

To be successful, a hub must develop four key attributes (Exhibit 2):

- **Presence.** A reputation as a world-leading hub and the infrastructure required to support and stimulate the innovative activities on which it focuses.
- **Connectivity.** The right people networks to link new enterprises, pharma companies, academia, government, and investment communities.
- **Capability.** World-class talent and the ability to acquire it locally.
- **Support.** Financial, regulatory, and professional support designed to provide the prerequisites for innovation.

Lessons for executives

We have drawn extensive lessons from our collaborations with governments and other stakeholders to build life science innovation hubs in Russia, Israel, Brazil, the US, Saudi Arabia, and the UK over the past few years. In our experience, pharmaceutical companies can improve their chances of success as hub investors or convenors by following a few key guidelines.

Pharmaceutical companies acting as hub *investors* would be well advised to:

Exhibit 2: Requirements for a successful hub

▪ International promotion by key opinion leaders, government, and top talent

▪ Incubator and wet-lab space

▪ Access to patient volumes (and associated data sets), particularly for highly specialized cases

▪ Ability to attract the best researchers globally in multiple areas of expertise

▪ R&D collaboration between academic and research institutions and large biomedical companies

▪ Strengthening top talent through company funding of university or institution education and research as well as development of commercial capabilities

Presence

Connectivity

Capability

Support

▪ “Can do” culture of bio-entrepreneurialism, often fostered through links with the business community

▪ Network events and competitions to promote collaboration, support entrepreneurs, and attract investment

▪ Encouragement of spin-outs from universities with technology transfer support including IP guidance

▪ Ability to perform animal research where necessary

▪ “Low hassle” planning permission, particularly for scientific facilities

▪ Network of angel and venture capital investors providing seed funding

Plan resource allocation to support the development of the hub where their involvement is low, and **consider committing more resources** if a substantial physical presence is necessary. To determine which level of involvement is appropriate, companies should identify technologies and therapeutic or disease areas that are critical to their success, ascertain which locations have emerging expertise and innovation



in these strategic areas, and then prioritize these locations by probability of success and other factors.

Engage the convenor to ensure they are linked into the developing strategic agenda for the hub. This is particularly critical for nascent hubs, where the convenor is likely to be the government. By getting involved early, companies should have the opportunity to guide the direction in which the hub develops as well as securing early access to innovation.

In cases where activity to develop the hub is limited, the company should **consider becoming the convenor**, especially if this gives it a major advantage in that location. It should link up with government to identify options for collaborating so as to accelerate the development of the hub and the industry. Once the company's interests are laid out and protected, additional companies can be brought on board to share the investment risk.

The messages for companies seeking success in the *convenor* role are:

Consider the hub's location and target sector and revisit them from time to time. Public initiatives often jump onto a successful bandwagon, and many attempts have been made to create an innovation hub in an underperforming economic location or in the latest growth sector regardless of whether the area meets the basic requirements for a hub.

Recognize the appropriate level of commitment from stakeholders.

Governments often under- or over-commit to entrepreneurship initiatives. Under-commitment leads to limited or curtailed impact; over-commitment crowds out the private sector, again curtailing entrepreneurial activity.

Understand and communicate the timescale needed for success.

Creating an innovation hub is a long-term process, whereas political cycles are biased toward short-term results. That means that initiatives are often cancelled or changed before they have had time to develop properly.

Take care with the threshold requirements for companies to qualify for initiatives.

In many entrepreneurship schemes, the requirements for participation have excluded the intended target companies. Strict stipulations on size and ownership have meant that many small high-tech businesses have been rejected for programs or have not even applied.

Don't focus exclusively on local development.

Initiatives need to encourage investment from and links with other hubs around the world.

To ensure that the hub has the maximum economic impact, don't neglect the wider context.

Many of the ideas discussed here can be extended to promote entrepreneurship beyond a particular innovation hub.

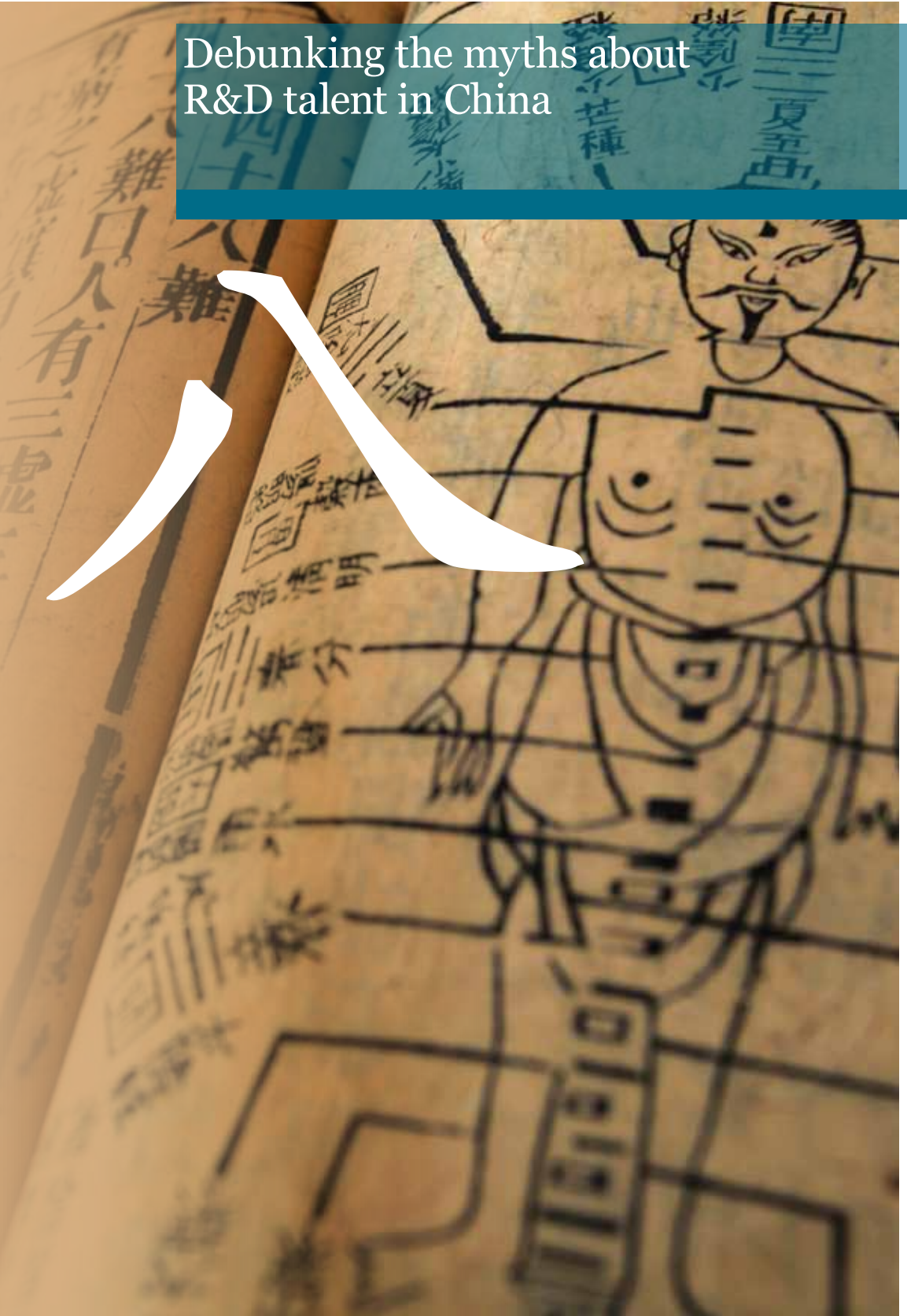


The long-term sustainability of the pharmaceutical industry will largely depend on the ability of life sciences to find a more efficient way of innovating. Local innovation hubs have driven economic, scientific, and technological advances for years. By organizing around these hubs and perhaps even playing a role as a catalyst within them, pharmaceutical companies could improve their ability to source and drive innovation in a more sustainable way.

Note

¹ See, for instance, Daniel Isenberg, “How to start an entrepreneurial revolution,” *Harvard Business Review*, June 2010; Michael Porter, “Clusters and the new economics of competition,” *Harvard Business Review*, November 1998, “Location, clusters, and company strategy” in G. Clark, M. Gertler, and M. Feldman (eds), *Oxford Handbook of Economic Geography*, Oxford University Press, 2000, and *The Competitive Advantage of Nations*, Free Press, 1990; and P. Krugman, *Geography and Trade*, MIT Press, 1991.

Debunking the myths about R&D talent in China



As major global pharma companies look east to build new R&D facilities, they should be wary of conventional wisdom about conditions in China. To get the most out of their investment, they will need to pay close attention to their talent development practices.

Cornelius Chang, Jay Chiang, Keith Lostaglio, Laura Nelson Carney, Jeremy Teo, and Fangning Zhang

Multinational pharmaceutical companies are scaling up their R&D organizations in China like never before, driven by the country's growing strategic importance, the size of its market, and the desire to access its promising talent. By 2016, more than four out of five global life science organizations are expected to be conducting R&D activities in China and other emerging markets. Meanwhile, China's scientific and technical capabilities are getting stronger and IP protection is improving.

Over the past five years at least nine major multinational companies (MNCs) have announced pharmaceutical R&D investments in China in excess of \$100 million, taking total investment in the country over the period to more than \$2 billion. Earlier investments in R&D sites in China in the 1990s were motivated partly by the desire to access lower-cost labor. More recent investments have been driven by the promise of access to innovation as well as China's increasing importance as a commercial market. The motives and the scale of ambitions vary, but many companies want to progress from "made in China" to "innovated in China" by conducting research into new medicines here and opening up access to local markets.

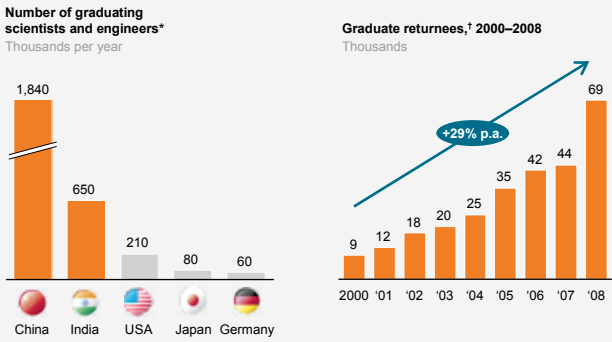
As a result, Chinese R&D sites are opening or growing almost as quickly as European and US sites are closing or shrinking.¹ MNCs have announced plans to hire more than 4,000 specialist scientists in the Shanghai area alone in the next few years. Although the opportunity is enormous, seasoned R&D leaders in China have no illusions about how difficult it will be. Finding, managing, and retaining R&D employees has become one of the toughest managerial challenges for pharma companies in China.

On the one hand, multinationals are rapidly expanding their R&D capacity: notable examples include Novartis, making a \$1.25 billion investment in building a new R&D center and adding 1,000 staff at an existing center; GlaxoSmithKline, which is taking its Shanghai research center to 1,000 staff; and Pfizer, which is building a new research center in Wuhan and will employ 540 staff between this and its Shanghai site. On the other hand, local players are also embracing innovation as the engine of the next wave of growth and increasing their own R&D spending. The government has identified biomedicine as a pillar industry in its twelfth five-year plan, and has announced a \$6 billion investment to support breakthroughs in drug development, process improvement, and technological innovation. All this adds up to rapidly escalating competition

for China’s R&D talent, resulting in a shortage of professional expertise that threatens to put a brake on MNCs’ growth ambitions.

However, the realities on the ground are not always visible to pharmaceutical executives at headquarters, and they risk being misled by a number of common misunderstandings about R&D talent in China. Below, we debunk eight of the most widespread myths.

Exhibit 1: China’s talent pool



* Including life sciences, mechanical engineering, and IT at bachelor degree level or higher, 2005
† Chinese nationals returning home after being educated and/or working abroad
Source: Division of Science Resources Statistics (SRS), NSF; US Institute of Applied Manpower Research; Eurostat; Shanghai Academy of Education and Science

Myth 1: China has a large and growing pool of highly trained scientists, so staffing an R&D site is easy

The reality could hardly be more different. Many multinational companies report they find it difficult to attract managers in China, and executives frequently cite persistent or rising employee turnover as their top talent challenge.

It is true that China has a huge working population and a relatively large number of graduates and PhDs in life sciences (Exhibit 1). Even so, much of the workforce is relatively raw and poorly suited to working in multinational pharmaceutical companies. A 2005 McKinsey Global Institute survey found that only about 10 percent of scientists and engineers graduating from Chinese universities were ready for the MNC workplace, a proportion that is unlikely to have improved much in the intervening years.² Because the Chinese educational system has a theoretical bias, students here spend less time on practical projects and teamwork than those in the west do.

Thus Chinese students may graduate with little experience of applying academic knowledge in an industry setting, little or no managerial experience or business knowledge, and little familiarity with the product development process, as well as limited English skills.

The implications for MNC R&D operations are profound. First, competition for the best talent from top universities will grow still more intense. Second, companies will have to invest more heavily in in-house training to ensure that recent graduate hires become productive staff.

Heads of R&D in China report difficulty in hiring management-level employees with sufficient scientific and leadership experience, and find it hard to scale up sites as fast as global HQ would like them to. The most difficult challenge of all is finding the right head of R&D for China: someone who can lead large teams effectively from discovery through late-stage clinical trials, drive great science, constantly recruit more staff, and at the same time negotiate the regulatory and

“Leaders with balanced skills and experience to manage the scientific and business aspects of drug R&D [are hard to find]. In addition, they also need to be comfortable operating in a highly dynamic environment.”

Steve Yang, VP and head of R&D for Asia and emerging markets, AstraZeneca³

“A lack of specialists and innovative talent in some key fields has become a bottleneck in China’s goal to build an innovative country.”

Yin Weimin, minister of human resources and social security⁴

cultural complexities of China as well as its medical affairs and IP challenges.

At operational level retention is even tougher than hiring, so frantic is the competition among companies for experienced staff, particularly biologists and clinical research associates. Pharmaceutical companies and contract research organizations (CROs) have been settling for hiring clinical research associates with less than a year of experience, and can expect attrition of 30 to 40 percent per year among this group. As MNCs expand their research organizations over the next few years, the talent pinch is expected to shift to pharmacologists, toxicologists, and chemists.

Recruitment and retention are growing ever more difficult and costly, especially for experienced managers and senior scientists. Many top graduates prefer to join state-owned enterprises or Chinese companies, where the pay is

comparable and the career opportunities and cultural fit are superior.

Paradoxically, much of the best Chinese drug discovery talent is still found in the US and Europe. MNCs often use overseas Chinese pharmaceutical associations as a channel to access talent: examples include the Sino-American Biomedical and Pharmaceutical Professionals Association (SABPA), the Sino-American Pharmaceutical Professionals Association (SAPA), BayHelix Group, the Chinese Biopharmaceutical Association (CBA), and the Chinese American Biopharmaceutical Society (CABS).

Myth 2: R&D operations are much cheaper to run in China than in Europe or the US

It’s true that R&D labor costs used to be far lower in China than in Europe and the US, but the gap is narrowing and R&D leaders no longer consider cost savings as a key reason to invest in China R&D. For management-level staff working at MNC R&D sites in China, packages have reached 75 percent of those in the west, and for leaders at VP and site-head level, compensation is as high or even higher in China than in Europe and the US. Compensation for junior staff is rising too: for instance, the estimated cost of employing bench chemists is expected to increase at a compound annual growth rate of 6 to 12 percent over the next five years. At present the average annual cost for these staff is running at 36 percent of the US level, but we calculate it will have risen to between 43 and 58 percent by 2015.

Over the long term companies may shift part of their workforce to tier 2

and tier 3 cities where labor costs are lower. Pfizer, as noted above, has recently established a clinical center in Wuhan.

Myth 3: Attracting and retaining talent is all about compensation

Attrition rates are relatively high in China. Many staff leave in pursuit of higher pay at competitors, leaving some companies with attrition of 10 to 20 percent a year. Compensation is widely taken to be one of the biggest obstacles to recruitment and retention. In one survey, 55 percent of MNC companies in China reported that their primary recruiting challenge was their inability to meet candidates' salary expectations, and 38 percent said they were unable to meet benefit expectations.⁵

However, pay is only one means to attract and retain talent. Other key elements of an employer's value proposition for staff include an *engaging job* with opportunities for accomplishment, variety, interesting challenges, a degree of autonomy, and flexible work conditions; an *exciting reputation* that makes employees feel proud to work for the company and enables them to balance their work and personal lives, support a good lifestyle, and feel stable and secure; an *energizing culture* with strong managers, great company leadership, and a congenial and creative workplace; and *effective talent management and development* where individuals have opportunities to grow and advance, to work in compatible groups and teams, and to have their individual contributions recognized. When these four elements are strong they may be just as important to staff as salary and benefits, but if they are weak employees may be tempted to leave for marginal increases in compensation elsewhere.

Where attracting talent is concerned, another survey found that local job applicants in the Asia Pacific region were much more likely to be deterred by perceived weaknesses in a prospective employer's corporate reputation or culture (cited by 39 and 36 percent respectively) than by the compensation package they were offered (cited by 7 percent).⁶ The same survey found that an individual's job profile, the profile of their direct manager, and the development opportunities available to them are the leading factors prompting executives to make a career move.

"Why do P&G people still make 30 percent less than those at competitors in China—and work there for several years? The reason is learning. P&G has very good training programs and very specific career development."

Benjamin Zhai, principal,
Egon Zehnder⁷

Myth 4: Other MNCs are the main threat in retaining talent

In the past R&D staff attrition was mostly driven by competing MNCs, since Chinese pharma companies and CROs were regarded as less prestigious employers. However, R&D leaders have recently seen top staff depart for domestic companies and CROs. With the inclusion of biomedicine as a strategic industry in the twelfth five-year plan and the government push for more innovation in Chinese companies, the profile of domestic pharma is changing. Rapid growth, the promise of a future IPO, and the potential for dramatic increases in compensation

and impressive job titles are now luring scientists at all levels to domestic players.

Notable examples at senior level include George Chen's move from J&J and Sanofi-Aventis in Shanghai to become chief medical officer at Beigene, and Weiguo Su's move from Pfizer in the US to the post of executive vice president of drug research at Hutchinson MediPharma in Shanghai. As domestic companies diversify beyond active pharmaceutical ingredients (API) and generics into innovative research, perceptions of the quality of their science and innovation are also changing.

Similarly, Chinese CROs are becoming increasingly successful at hiring top talent from MNCs as perceptions of the quality of their science shift and as they make sustained investments in career development programs.

Myth 5: R&D sites in China should operate like those in Europe or America

The pharmaceutical industry is still working on the assumption that the way that western R&D sites have been discovering drugs for the past three decades is the right way. This is despite endless discussions in recent years about the ills besetting R&D research: waning productivity, rising costs, and declining numbers of drug approvals.

If the industry adopts the same approach in China it will continue to get the same results. It's clear that established methods of drug discovery and development will not serve it well in the future. Some companies in the US and Europe are experimenting with alternative models but change is

difficult, particularly when it requires R&D staff to change their mindsets.

MNCs with R&D sites in China have a rare opportunity to experiment with radically different models. These sites are smaller (typically with fewer than 200 people), more recently established, and unfettered by the red tape and legacy of major sites in the west. Global R&D leaders could allow their China sites more freedom to try out new and better ways of doing drug discovery and development — new ways for project teams to work together, to identify and validate novel targets, to get an early clinical read on efficacy, and to kill projects sooner.

Whether Chinese sites should run like their western counterparts is one question; whether they *can* is quite another. Chinese employees interact with each other and with their bosses in quite a different way from what we see in the west. It is important to build local cultural norms into working patterns and performance recognition if Chinese employees are to be comfortable, creative, and productive.

Moreover, the culture of scientific apprenticeship that is so central to successful drug discovery groups is proving harder to build in Chinese R&D sites because there are fewer seasoned drug hunters to go around than in the US and Europe. High levels of technical skill and rules-based decision making are only half of the recipe; learning the art of drug discovery and judgment-based science through experience will also be essential for success. However, some Chinese sites may be close to the tipping point in this respect: it takes only a handful of experienced drug discoverers who are also exceptional leaders to enlighten and inspire a whole site.

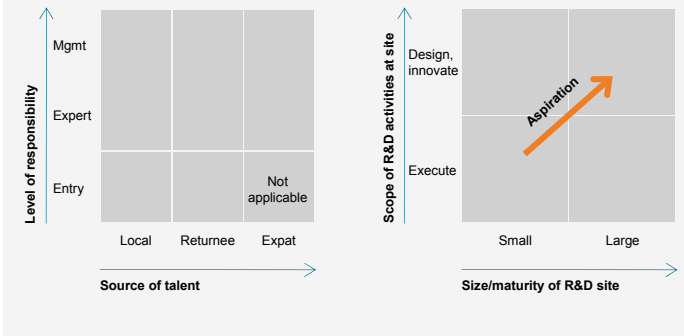
Myth 6: A single talent strategy will suffice for expats, returnees, and local hires

This is far from being the case. Building an effective talent management strategy in China involves thinking carefully about how to tailor attraction and retention initiatives to the different needs of expatriates, returnees, and local hires. Because of their contrasting educational and work experiences and cultural backgrounds, each group has its own strengths, weaknesses, and expectations.

Expat staff are often managers brought in from headquarters in the west. They typically maintain a strong connection with the corporate center and ensure that its philosophy is implemented at the Chinese site. By controlling and improving local skills, they uphold high company standards. On the downside, they may have little understanding of local culture, language, or relationships, and their compensation packages tend to be very expensive. Some expat staff come from other Asian countries and will be slightly more comfortable with Chinese culture than westerners are, but differences still remain and should not be underestimated, particularly since local staff are likely to be less tolerant of shortcomings in communication or leadership on the part of Asian managers than they would be with Americans or Europeans. Asian expats tend to be less embedded in the corporate culture and a little less expensive than their western peers.

Returnees—China-born individuals who have studied or worked in the west—have the advantage of familiarity

Exhibit 2: Tailoring talent strategies to target groups



with both Chinese and western languages and cultures. They are less involved in the corporate culture, but also less expensive than expats.

Locals who were born and educated in China have strong local connections, and are likely to be of a high caliber if hired from the top universities. Most lack strong English skills and international exposure and have little involvement in the company culture, but they are the least costly of the three groups.

The best approaches to attract talent from these three groups will also depend on the size and strategy of the site concerned. The factors MNCs need to consider when devising tailored talent strategies are illustrated in Exhibit 2.

The right balance between expatriates, returnees, and local hires will vary by company depending on its corporate culture, local leadership style, and ambitions, the degree of autonomy the site has from global control, and many other factors. There is a growing trend to replace expats with local and returnee employees, especially among companies with a long-established China presence and even at the most senior level (Exhibit 3).



That said, pharmaceutical R&D does have opportunities to learn from other industries. In particular, two companies stand out as having best-in-class R&D talent management approaches in China: GE and GM.

GE offers R&D talent a prestigious career development path with two tracks. The scientific track offers a path to become a senior principal scientist with deep technical knowledge who has significant decision rights in projects. The

management track offers graduates roles as scientists with scope to advance to laboratory or global technology manager for a particular field. Employees at each level have a clear set of evaluation criteria and a reward system to recognize their individual contributions, and some graduates who start in the scientific track have the option to switch to management if they decide they want to gain more exposure to the business. These attractive and flexible career paths, coupled with GE's reputation, enable the company to attract top talent from leading Chinese universities year after year.

Hiring and talent development are also great strengths at GM. It builds Chinese graduates' skills and knowledge through a suite of development programs that include coaching, stringent technical and leadership training, and mentoring. The company also sponsors professors and departments at leading universities to research topics of interest to GM as part of applied engineering programs. This enables the company to train students as R&D interns and to develop good recruiting relationships with their institutions. Many

Myth 7 : Pharmaceutical R&D in China presents such a unique set of talent challenges that it can learn nothing from other industries

It is true that many aspects of drug discovery and development mark pharma R&D out from that in other industries. For one thing, the R&D productivity crisis is putting a great deal of pressure on China to become a new frontier for innovation. In addition, the innovation cycle is far longer and more expensive in pharma than in consumer packaged goods, high tech, telecommunications, software, automotive, and other R&D-intensive industries, and individual projects have a much lower probability of success. Biological rather than consumer insights drive drug discovery and call for specialists with deep experience. Compared to other industries, pharma also need a wider range of highly developed technical disciplines to make its R&D engine run, and relationships with leading academics matter more down the entire value chain from R&D to marketing.

of the interns are hired after graduating. Managers also benefit from the chance to evaluate and train the interns.

Pharma R&D leaders can learn from these and other companies. Recognizing R&D staff for their strengths, setting clear expectations for the skills required at each level, crafting flexible career paths, establishing extensive development programs, providing strong mentorship, and using internship programs to try out new staff are best practices across industries, but strikingly absent in many pharma R&D organizations in China.

Myth 8: All we need to do is hire the best scientists

Despite the recent rapid growth and heavy investment in R&D sites in China, many MNCs are woefully underinvesting in talent management. Global leaders and boards are keen to see rapid scale-up at their sites, but in the scramble to hire talent and get operations under way many companies are failing to pay enough attention to their people. Staff often lack clarity over roles, career paths, and development opportunities, and dissatisfaction and attrition are high. Employees complain that they feel frustrated, are treated as second class—deprived of access to the training, development, and international opportunities enjoyed by their colleagues in the US and Europe—and feel as though they are in limbo, lacking clarity on personal objectives, organization structure, reporting lines, and company strategy.

Improving people development programs will be critical. At the most basic level, this is about applying the same best practices in Chinese sites as in the rest of the world. Obvious though this may seem, it is not

common practice. MNCs must keep investing to develop a compelling employee value proposition that provides strong reasons for top R&D talent to join them and stay with them. This must include the four elements discussed earlier: an engaging job, an exciting company reputation, an energizing culture, and effective talent management and development.

Beyond this, MNCs sorely need more programs to mould and develop new hires fresh from leading Chinese universities. Such programs should introduce them to the corporate culture, teach them the drug discovery process, provide whatever English-language training they need, and develop their management and leadership skills. Strong scientists become project leaders sooner in China than they would at a larger European or US site, yet they seldom have training on how to perform their role or mentors to learn from.



Most observers agree that pharmaceutical companies will take major steps to the east in the next ten years, not just for reasons of cost but increasingly for talent too. The challenge for the industry is to make this transition at a time when its R&D operating model is coming under mounting pressure. The most successful companies will manage to globalize toward Asia and reinvent their innovation engine at the same time, harnessing all the potential that China holds as part of new ways of working in R&D.

Notes

- 1 Recent announcements include the closure of Pfizer's site at Sandwich, AstraZeneca's Charnwood and Lund sites, and eight Merck sites in Europe and the US.
- 2 See Diana Farrell and Andrew J. Grant, "China's looming talent shortage," *McKinsey Quarterly*, November 2005.
- 3 Quoted in Ling Li, Lan Kang, and Shilpa Gentela, "China versus India: Reality check for pharma R&D," Korn/Ferry International, 2008.
- 4 Quoted in Chen Xin, "Lack of talent stifles progress," *China Daily*, October 23 2010.
- 5 Economist Intelligence Unit, *People for Growth: The talent challenge in emerging markets*, May 2008.
- 6 *Managing Global Talent Acquisition, Emerging Markets: SharpStream Life Sciences emerging market talent survey*, 2008.
- 7 Quoted in "Managing and developing talent in China and India," Development Dimensions International, 2006.

Cornelius Chang is a consultant in McKinsey's Sydney office, **Jay Chiang** is an associate principal in the Silicon Valley office, **Keith Lostaglio** is a principal in the Tokyo office, **Laura Nelson Carney** is an associate principal in the Hong Kong office, and **Jeremy Teo** is an associate principal and **Fangning Zhang** is a consultant in the Shanghai office. The authors would like to thank the heads of R&D in China who shared their insights with us in roundtable discussions.



Closing the R&D gap in African health care

A system governed by Africans in Africa is needed to provide a sustainable funding mechanism that would encourage African scientists to collaborate on common health concerns, share expertise, and build capacity.

Raymond De Vré, Emiliano Rial Verde, and Jorge Santos da Silva

The health status of Africans remains far worse than that of people in many other developing regions, to say nothing of Europe and North America. Although a lack of access to health care and serious health system deficiencies are important reasons for this phenomenon, other elements aggravate it. One is insufficient research and development aimed at addressing Africa's unmet health needs. The result is a lack of efficient therapies for many illnesses that affect that continent almost exclusively and are therefore beyond the scope of most research efforts in the developed world. Consequently, improving the health of Africans implies not only addressing the deficiencies of access and health systems but also stimulating the development of suitable drugs and diagnostics.

A look at the relationship between GDP per capita and life expectancies illustrates the magnitude of the problem. While the GDP of Africa as a whole has grown by over 200 percent in the past 20 years, only two extra years of life expectancy were added during that time. Asian countries with comparable GDPs per capita tend to have life expectancies 5 to 10 years higher than those of their African counterparts. Even high-GDP African countries, boasting per capita figures comparable to those of many countries in eastern Europe and South America, have life expectancies 10 to 20 years lower

than those of comparable nations in these other regions. Undoubtedly, Africa's weak health systems and HIV/AIDS epidemic are contributing to the problem. Yet several countries elsewhere with similarly weak systems or similarly burdensome HIV/AIDS rates, such as Jamaica and Thailand, still have life expectancies that are five to 25 years longer.

A big part of the problem is a lack of tools to diagnose and treat the diseases of Africa. Some available drugs addressing the diseases that affect Africa disproportionately are not fully effective and present high toxicity levels. Acquired resistance has made other therapies less effective.¹ Low levels of patient compliance because of the duration and complexity of certain treatments is another impediment.

What's more, diagnostic tools for some common diseases in Africa are hard or impossible to apply in the field or could be made more broadly usable in difficult environments. While emerging public-private partnerships between international organizations and pharmaceutical companies are making inroads, these efforts are still few and far between. In fact, only about 1 percent of new drugs developed from 1975 to 2004 treat diseases of the poor, although such diseases account for more than one-tenth of the global burden.²

Current R&D efforts aimed at treating African diseases mostly depend on organizations outside Africa. They try to find solutions for its pressing health needs but not to create a sustainable R&D structure on the African continent. To develop a plan for a pan-African health R&D project, McKinsey analyzed five years of health research output and scientific networks involving African scientists. As highlighted in other recent publications,³ we conclude that a system governed by Africans in Africa is needed to provide a sustainable funding mechanism that would encourage African scientists to collaborate on common health concerns, share expertise, and build capacity.

The challenges ahead

The argument for increased R&D to develop drugs and diagnostics for diseases that disproportionately affect Africa is compelling. Although promising trends are fostering the development of such an R&D capacity, the African countries responsible for the largest number of biomedical-research publications—such as Egypt, Nigeria, and South Africa—generate 15 to 150 times fewer research articles than leading developed countries do. More alarmingly, they generate 1.2 to 8.0 times fewer research publications than other developing countries, such as Argentina, Brazil, India, and Thailand. These figures indicate that while research to treat predominantly African diseases and conditions is being conducted, major challenges still prevent these efforts from reaching sufficient scale and productivity.

A significant knowledge gap

Many diseases with a high prevalence in Africa are either almost exclusive to it (for example, onchocerciasis,

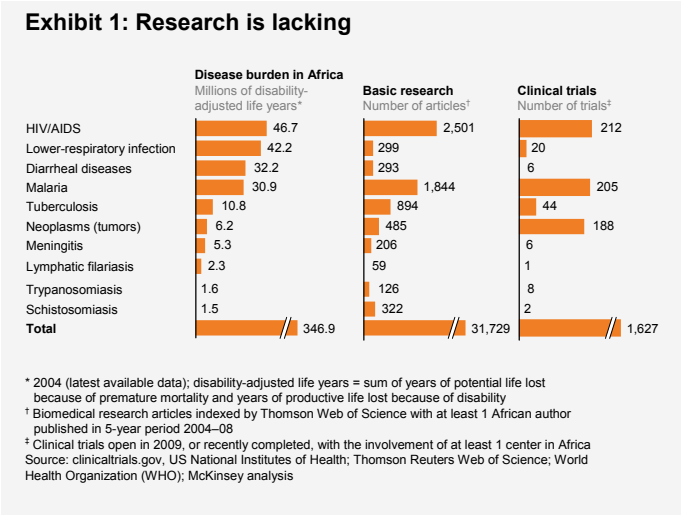
human African trypanosomiasis, schistosomiasis, and malaria) or affect the continent disproportionately (HIV/AIDS, ascariasis, meningitis, trachoma, lower-respiratory infections, diarrheal diseases, leishmaniasis, tuberculosis, and lymphatic filariasis). World Health Organization (WHO) estimates indicate that this group of diseases accounts for more than half of Africa's total disease burden. Accurately quantifying their economic impact is difficult, but rough estimates show that they reduce the continent's GDP by as much as 20 percent, or \$200 billion, a year.

Despite the terrible impact these diseases have on Africa's economic development and welfare, they have been seriously under-researched: with the exception of HIV/AIDS and malaria, the pipeline of products aimed at treating them is just about empty (Exhibit 1). Their almost exclusively African incidence means that interest from the international research community is low, which emphasizes the need for drugs and diagnostic R&D efforts owned by Africans.

A favorable trend is emerging, though. An analysis of five years of biomedical-research articles originating in Africa shows that the number of articles on different diseases correlates well with their incidence in Africa.

A low degree of collaboration

The productivity of R&D efforts, both public and private, is maximized by harnessing the synergies generated by networks of scientists with complementary skills and capabilities. These collaborative networks also benefit when expertise is transferred from one network member to another, which builds capabilities and increases the network's capacity. In academic environments, the availability of funds drives the creation and work



2008 (a total of 31,729 articles involving 20,714 institutions) confirmed this trend. More than 92 percent of the institutions that collaborated with the 20 most productive and collaborative institutions in Africa were either from the same country or from outside Africa. In fact, while most publications result from collaboration, scientists from more than one African country worked together in only 5 percent of cases. Notably, only 5 percent of the patents granted to African inventors

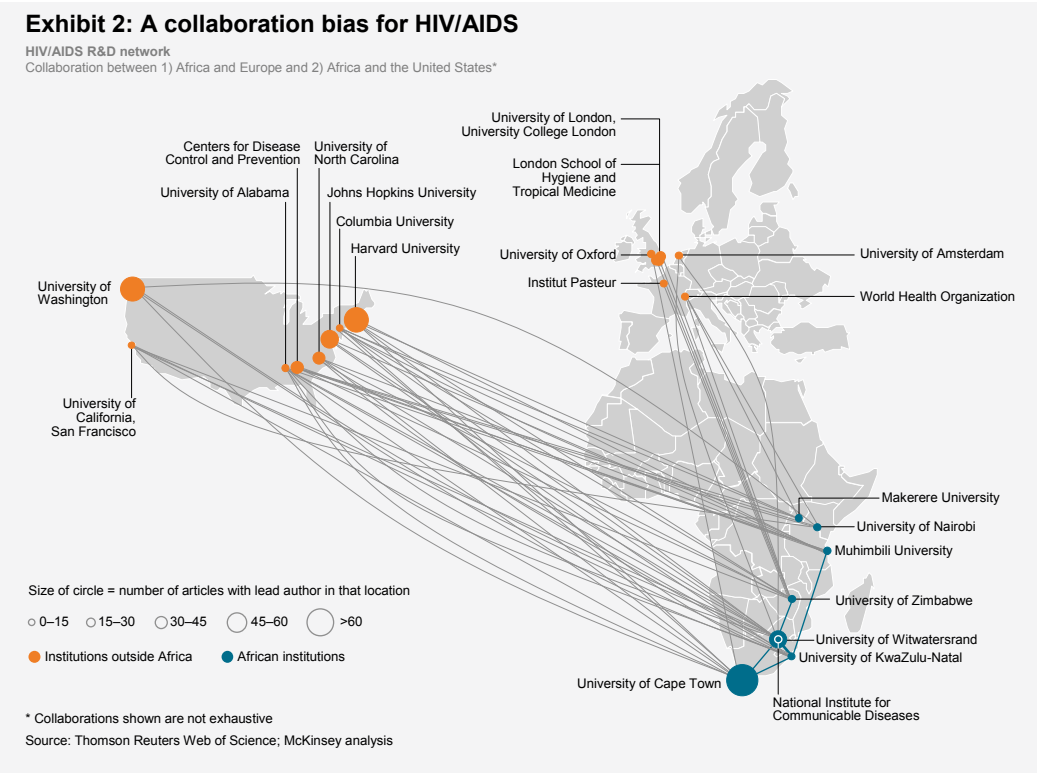
of collaborative networks, so African scientists strongly tend to collaborate not with one another but with scientists in Europe and the United States, where research funding and technology are more readily accessible. In fact, only 10 percent or less of R&D funding at many public-health research centers in Africa is local; the rest comes mostly from the United States and Europe, either directly or through collaborations.

resulted from collaboration between inventors in more than one African country.

Our analysis of Africa’s research output in 17 selected disease and functional areas shows the low degree of collaboration within the continent, despite the substantial number of centers publishing in collaboration. For malaria, a total of 1,844 research articles from 2004 to 2008 had at least one African author. Of these articles, over 40 percent had a lead author from Africa, and most were published collaboratively. Despite the importance of malaria in many African countries, however, only 13 percent of these articles involved collaboration between authors in more than one African country.

Exhibits 2 and 3 show the most productive and collaborative institutions publishing with the involvement of at least one African scientist in HIV/AIDS and malaria networks respectively. The links between these institutions were traced (through coauthorship), and the circles marking their locations were sized according to the number of articles led by an author from a given location. While there are some links between African institutions, suggesting a degree of local collaboration, the exhibits show that collaboration is clearly biased toward Europe and the United States. Although HIV/AIDS (Exhibit 2) is an area of great interest for both developed and African countries, diseases that mostly affect Africa, such as malaria (Exhibit 3), show the same pattern. That bias represents a major challenge because it has the effect of fostering the misalignment between medical research and Africa’s health priorities, and prevents Africans from driving the research agenda.

A more exhaustive analysis of all the African biomedical-research output from 2004 to



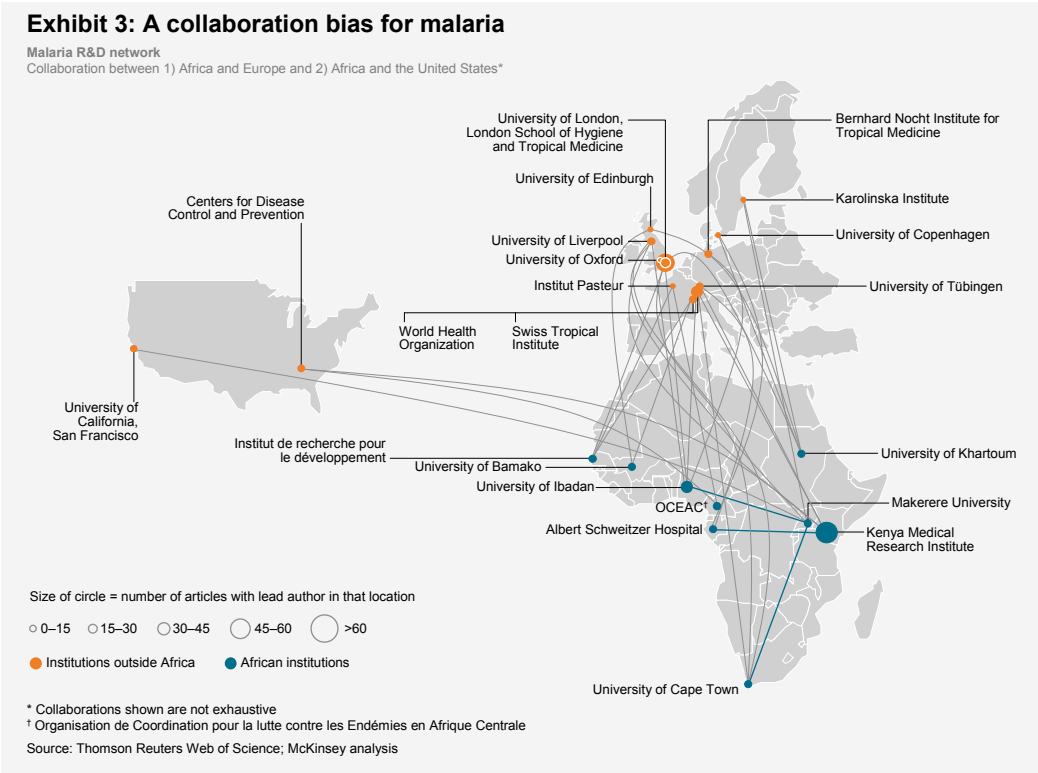
Despite the low degree of collaboration within Africa, several countries there have a pool of human capital and a number of research centers that could collectively form strong R&D networks. A few established African research centers have a wide range of expertise: they participate in efforts that, although linked to the developed world, generate significant numbers of research articles. These centers are also true originators of research and central elements of global collaborative efforts. The existence of such high-quality, productive, and connected institutions in Africa indicates that active R&D networks could and should be formed there and eventually carried to scale.

Insufficient investment and ownership of R&D

Lifting the health status of whole populations involves concerted efforts

by governments and other local stakeholders, including the private sector, the research community, and influential individuals. As long as the bulk of R&D investment comes primarily from foreign sources, alignment between local R&D efforts and local priorities will remain difficult to achieve—a situation that demands attention from African governments but, by and large, hasn't received it.

Africa as a whole lags behind the world's other developing regions, such as South America and southeast Asia, in overall R&D spending per capita. Moreover, great disparities exist among subregions within Africa itself. While the southern region invests, on average, more than the world median in R&D, western and central Africa present a grim picture when compared with other parts of the developing world and the



rest of Africa. This intra-African inequality magnifies the funding-gap challenge.

The need to increase R&D expenditures for health is well recognized. The African Union has set a target: to dedicate the equivalent of 2 percent of total healthcare spending to health research by 2015, which represents 0.1 percent of GDP and 33 percent of overall R&D. Kenya now spends 0.15 percent of GDP on health research, so 0.1 percent is a plausible target. In fact, some African countries are aggressively increasing their total R&D expenditures. South Africa, for example, will soon be devoting 1 percent of its GDP to R&D. Egypt spent 0.6 percent of GDP on R&D in 2010 and hopes to reach 1 percent by 2017.

Ownership of the R&D process is a concern as well, not only because funding

is now primarily external, but also because Africans are seriously under-represented in organizations devoted to Africa's health problems. Only 9 to 14 percent of the board members of international organizations focused on HIV/AIDS, tuberculosis, and malaria, for example, are Africans.⁴ Although these organizations have been very successful, local ownership of the research agenda is necessary to meet local health needs sustainably.

Building innovative networks

The solutions to these issues lie within Africa. Their paramount objective is to develop a self-sufficient, sustainable, and pan-African R&D system that could address not only today's problems but also evolving public-health issues.

The key is to harness the untapped power of collaboration among African researchers by forming and supporting networks of research groups in Africa (such as ANDI, the African Network for Drugs and Diagnostics Innovation). This model, recently endorsed by the African research community,⁵ would turn laboratories that complement each other technically and functionally into cohesive networks engaging in projects specifically aimed at developing new tools to address African diseases.

This approach would promote African research agendas and local ownership, since such networks would be formed by investigators working in Africa and cooperating to advance their own local scientific interests. Financial support for these networks would also develop the capabilities of local scientists and improve Africa's health R&D infrastructure.

To ensure that drugs and diagnostics advance along R&D pipelines, the proposed network-based model should adhere to these principles:

1. Strong project-management coordination for each network to ensure timely progress. A broad view of these networks' project portfolios will be needed to prevent duplication and ensure that synergies are captured.
2. Significant project funding through five-year renewable grants, which would change the culture of short-term research grants now widespread in Africa. Such funding cannot be provided through typical yearly donor campaigns, but will require a sustainable, proven solution, such as the establishment of an independent, professionally managed endowment fund.

3. Additional grants to upgrade the facilities and equipment needed to improve the way a project network functions.
4. Better intellectual property management that responds to the needs of inventors and the African public, perhaps through pan-African technology-transfer offices analogous to those of major research universities.
5. Increased ownership by key stakeholders in Africa, as well as efforts by public and private organizations to guarantee that the drugs and diagnostics developed by these networks will move into production.



The approach outlined above focuses on bringing Africa's researchers together into regional networks to harness the capacity and capabilities that now exist on the continent. By involving local stakeholders, it seeks to improve the likelihood that specific initiatives will be aligned with African health priorities. Moreover, it aims to create a sustainable stream of projects that could develop new health tools.

Successful implementation will require a concerted effort based in and led by Africa and supported by the international community. The approach aims to avoid competition between the new research networks and existing players, to create partnerships that would prevent the duplication of effort, and to make products easier to develop and access.

Notes

- 1 "Research and development for neglected diseases—Lessons learned and remaining challenges," International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), 2005 (www.ifpma.org/documents/nr4959/neglecteddiseases_finaldoc2005.pdf).
- 2 Pierre Chirac and Els Torreele, "Global framework on essential health R&D," *Lancet*, 2006, Volume 367, Number 9522, pp. 1560–61.
- 3 Tom Mboya-Okeyo, Robert G. Ridley, and Solomon Nwaka, "The African network for drugs and diagnostics innovation," *Lancet*, 2009, Volume 373, pp. 1507–08; *Strategic and business plan for the African Network for Drugs and Diagnostics Innovation (ANDI)*, World Health Organization, October 2009; and Solomon Nwaka et al., "Developing ANDI: A novel approach to health product R&D in Africa," *PLoS Medicine*, June 2010, Volume 7, Number 6: e1000293.
- 4 T. J. Tucker and M. W. Makgoba, "Public–private partnerships and scientific imperialism," *Science*, 2008, Volume 23, Number 320, pp. 1016–17.
- 5 Second ANDI (African Network for Drugs and Diagnostics Innovation) Stakeholders Meeting, Cape Town, South Africa, October 4–7, 2009.

This article was first published in the June 2010 issue of *McKinsey Quarterly*.

Raymond De Vré is a principal and **Emiliano Rial Verde** is a consultant in McKinsey's Geneva office; **Jorge Santos da Silva** is a consultant in the Zurich office.

The background of the page is an abstract composition. It features a dark, textured brown base, possibly representing aged paper or a natural material. Overlaid on this are large, flowing, teal-colored shapes that resemble liquid or organic forms. A horizontal teal band is positioned across the upper portion of the image, serving as a backdrop for the section header. The overall aesthetic is organic and artistic.

About the authors

The authors of these articles represent a cross-section of McKinsey’s global Pharmaceuticals and Medical Products R&D Practice. We welcome your thoughts and reactions to the ideas presented here.

To share your comments or obtain more information, please email us at life_r&d@mckinsey.com or contact the authors individually. The email addresses of McKinsey authors follow the pattern forename_surname@mckinsey.com.

McKinsey & Company is a global consultancy firm that helps leading corporations and organizations to make distinctive, lasting, and substantial improvements to their performance. McKinsey advises companies on strategic, operational, organizational, and technological issues. Of our 8,000 consultants worldwide, 1,700 focus on health care, and 28 percent of them hold PhD or MD degrees. In the past four years we have completed more than 4,000 engagements in health care, spanning all major sectors and functions of the industry.

McKinsey’s Pharmaceuticals and Medical Products R&D sub-practice supports a wide range of clients on pharmaceutical R&D issues, including major pharmaceutical companies, biotechnology players, medical device firms, clinical research organizations, and government agencies. In the past five years McKinsey has conducted more than 350 engagements with more than 50 R&D clients.

Heads of Pharmaceutical and Medical Products R&D Practice

Global and North America
Ajay Dhankhar

Europe
Matthias Evers and Martin Møller

London No. 1 Jermyn Street London SW1Y 4UH United Kingdom Tel: +44 (20) 7839 8040	Mumbai Express Towers 21st Floor Nariman Point Mumbai 400021 India Tel: +91 (22) 2 285 5532	New Jersey 600 Campus Drive Florham Park NJ-07932 United States Tel: +1 (973) 549 6600	New York 55 East 52nd Street 21st Floor New York NY-10022 United States Tel: +1 (212) 446 7000
Shanghai 17/F Platinum Building 233 Tai Cang Road Shanghai 200020 People's Republic of China Tel: +86 (21) 6385 8888	Silicon Valley 3075A Hansen Way Palo Alto CA-94304 United States Tel: +1 (650) 494 6262	Tokyo Roppongi First Building 9th Floor 9-9 Roppongi 1-chome Minato-ku Tokyo106-8509 Japan Tel: +81 (3) 5562 2100	Zurich Hotelstraße Zürich-Flughafen CH-8060 Switzerland Tel: +41 (44) 876 8000

