

Beyond borders

Matters of evidence

To our clients and friends:

Welcome to the 27th annual issue of Ernst & Young's biotechnology industry report.

Almost five years after the start of the global financial crisis, the challenges facing biotech companies have not diminished. Our analysis of 2012 trends suggests that many firms are still preoccupied with matters of efficiency: the quest to raise funds in a difficult financing environment and the need to deploy existing capital efficiently. In 2012, the "innovation capital" raised by biotech companies with revenues below US\$500 million remained virtually static at levels significantly below those of the pre-crisis years. Meanwhile, many smaller companies across the four established biotechnology centers (US, Europe, Canada and Australia) cut research and development spending during the year.

But even as firms continue to deal with *matters of efficiency*, a second trend is becoming more real by the day: the move to evidence-based health care systems in which reimbursement is obtained by demonstrating how products add value and improve health outcomes. Our analysis, based on a survey of US and European companies as well as in-depth interviews with a handful of venture capitalists and pharma business development executives, reveals that most biotech companies are not adequately prepared for this shift. To succeed in the new world of health care, companies will need to truly understand the experiences and needs of payers and patients – and make sure their products are demonstrably aligned with the "value leakages" that matter most to these two constituencies.

The need to focus on *matters of evidence* affects practically every biotech firm, regardless of size, location and stage of development. If you're an early-stage company, being unprepared with payer-relevant data could hurt your valuations in deal negotiations or venture rounds. If you're a platform company, you should prioritize the diseases in which your platform will be applied by assessing the payer environment and standards of care in each disease area. If you're a resource-constrained entity, it's all the more important that you allocate capital prudently, by targeting diseases and drugs in which you have the best shot at getting reimbursed. The question isn't whether you can afford to act on this imperative, but whether you can afford *not* to.

We look forward to exploring these topics throughout the year ahead via social media. Follow us on Twitter and join the conversation on our blog (LifeSciencesBlog.ey.com). Gain access to biotech data on our data site (ey.com/BiotechData).

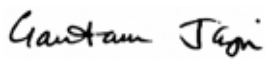
Ernst & Young's global organization stands ready to assist you in these challenging times.



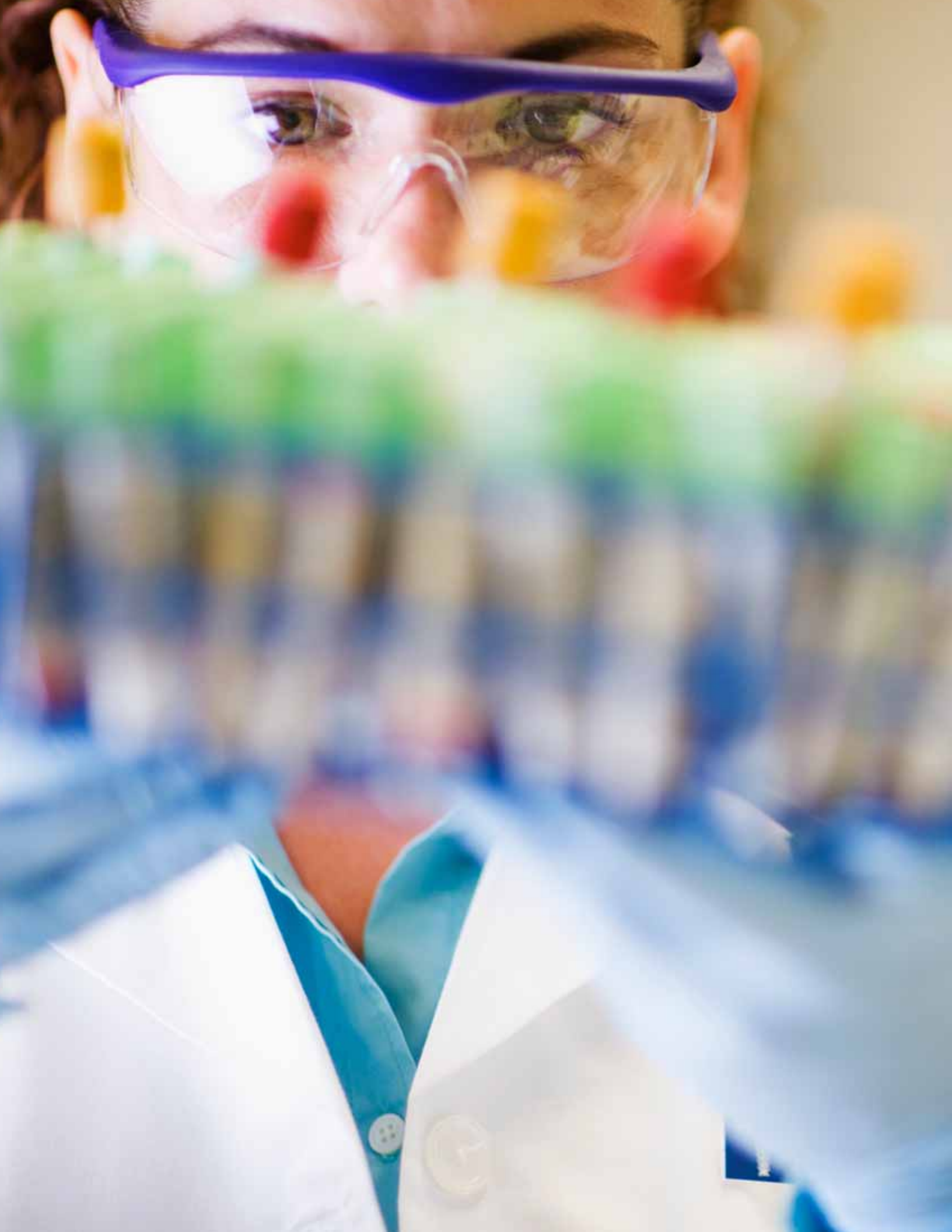

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Perspectives



Matters of evidence

Matters of efficiency

For the last three years, our *Point of view* articles have focused heavily on matters of efficiency – the need to do more with less and the measures companies and investors are undertaking to conduct research and development (R&D) more efficiently. This was only natural. After all, capital efficiency was the topmost concern for industry leaders in the aftermath of the global financial crisis, when a “new normal” emerged for capital markets, characterized by restricted access to funding for smaller companies.

We reviewed in some detail the steps venture capitalists and companies are taking – models such as fail-fast R&D, asset-centric funding and more. While these creative approaches are much needed, they are, as we pointed out in last year’s report, tinkering around the edges of an existing R&D paradigm that is now under unprecedented strain.

Last year, we discussed a model that could radically change R&D by taking a much more holistic approach to drug development, sharing information to learn in real time across the cycle of care and fundamentally changing how risk and reward are allocated. This approach, the holistic open learning network, or HOLNet, involves a broad spectrum of entities (biotech and pharma companies, payers, providers, disease foundations and potentially others) collaborating in “pre-competitive” spaces to share data and establish standards. We continue to think that these consortia have the potential to change the R&D paradigm from one that is linear, slow, inflexible, expensive and siloed to one that is iterative, fast, adaptive, cost-efficient and open/networked.

When we launched last year’s report at the 2012 BIO International Convention

in Boston, we were very gratified to see that such approaches were already being discussed broadly. Nor was the interest limited to talk. With the convention as a backdrop, the Government of Massachusetts and seven biopharmaceutical companies announced the formation of the Massachusetts Neuroscience Consortium. The consortium is funding results-oriented research projects and developing common standards, and is committed to sharing results with all participants. Clearly, the time for rethinking R&D has arrived. Companies large and small are receptive to, and proactively exploring, more open approaches to innovation.

But the focus on efficiency is just one of the two huge challenges facing biotech companies. ... The other is the move to outcomes-focused, evidence-driven health care systems.

In the year since, we have seen HOLNet-like approaches gain traction. A few months after the BIO Convention, 10 of the world’s largest drug development companies combined forces to create TransCelerate BioPharma. TransCelerate aims to make R&D more efficient through initiatives such as developing new standards for recording clinical trials, qualifying trial sites and training investigators. Several big pharma companies and the Hamner Institutes for Health Sciences formed the DILI-sim Initiative, a pre-competitive partnership, to conduct predictive modeling assessing whether new drug candidates are likely to cause drug-induced liver injury in patients. The modeling software would be made openly available. Meanwhile, a number of other consortia expanded their memberships and/or announced

new initiatives. These are all positive developments and we are encouraged by adoption of more open, collaborative, real-time approaches to conducting R&D.

But the focus on efficiency is just one of the two huge challenges facing biotech companies in the current business environment. The other is the move to outcomes-focused, evidence-driven health care systems. As health care costs rise at an unsustainable rate, payers are changing incentives to reward participants across the health care system based on the demonstrable value they deliver (this is often referred to as a move away from fee-for-service or fee-for-product and toward pay-for-performance).

Indeed, 2012 did not just see progress on the HOLNet front. This was also the year in which a favorable judgment by the US Supreme Court and the re-election of President Obama removed any lingering doubt that the Patient Protection and Affordable Care Act (ACA, sometimes referred to as “Obamacare”) is now the law of the land. For better or for worse, the world’s largest health care market is inexorably moving down a path of expanded access and experimentation with new approaches to lowering costs. The ACA encourages the adoption of new holistic models for care such as accountable care organizations (ACOs) and patient-centered medical homes (PCMHs). These models are gaining traction. A study released in November 2012 found that an estimated 10% of the US population is already covered by ACOs – a mere two years after the concept was first introduced.

While these are important changes in the world’s largest health care market, things are even further along in Europe, where payers have been embracing evidence-



Selected recent risk-sharing agreements

Drug	Indication	Company	Year	Agreement with	Market	Description
Cimzia (certolizumab pegol)	Rheumatoid arthritis	UCB	2010	NICE/NHS	UK	UCB pays for the first 12 weeks of therapy for all patients; after that, NHS pays for responding patients
Vidaza (azacitidine)	Myelodysplastic syndromes/ chronic myelomonocytic leukemia/acute myeloid leukemia	Celgene	2010	AIFA	Italy	Celgene offers 11% rebate for patients not responding to three cycles of treatment
Votrient (pazopanib)	Kidney cancer	GlaxoSmithKline	2011	NICE/NHS	UK	12.5% discount to match price of Pfizer's Sutent; further rebates if Votrient is inferior to Sutent in ongoing head-to-head trials.
Rebif (interferon beta-1a)	Multiple sclerosis	EMD Serono	2011	Cigna	US	EMD Serono offers rebates based on outcomes (e.g., drug adherence, reduced ER visits/hospitalizations)
Votrient (pazopanib)	Advanced renal cell carcinoma	GlaxoSmithKline	2011	AIFA	Italy	GSK pays for patients not responding to 24 weeks of treatment
Mozobil (plerixafor)	Stem cell mobilization	Genzyme	2011	AIFA	Italy	Genzyme refunds entire treatment cost upon its failure
Autologous platelet-rich plasma gel	Chronic non-healing wounds	Cytomedix	2012	CMS	US	CMS' Coverage with Evidence Development program provides coverage while collecting clinical evidence on health outcomes

Source: Ernst & Young, press releases and media reports.

AIFA: Agenzia Italiana del Farmaco (Italian Medicines Agency), CMS: Centers for Medicare & Medicaid Services, NICE: National Institute for Health and Care Excellence, NHS: National Health Service.

based approaches for considerably longer. The UK has been using health technology assessments (HTAs) conducted by the National Institute for Health and Care Excellence (NICE) for over a decade, while Germany and other markets have also introduced similar approaches with various degrees of transparency. Risk-sharing agreements, in which manufacturers agree to take on some of the financial risk through mechanisms such as agreeing to cover the cost of non-responding patients, have become increasingly commonplace in Europe, often becoming the de facto price of entry for high-priced therapeutics in many markets. While the practice is widespread, our Ernst & Young colleagues, who are often at the front lines helping negotiate these agreements, report that a growing number of these agreements are confidential. (For a list of select risk-sharing agreements, see the chart above.)

These trends are also particularly salient for biotechnology, since specialty drugs are the biggest driver of costs in drug spending. Two recent studies conducted by pharmacy benefit manager Prime Therapeutics and Blue Cross and Blue Shield of Minnesota forecast

that specialty drugs will account for 50% of all drug costs by 2018, up from 20% in 2009. Since many of the diseases on which biotech firms focus are treated using specialty drugs, the level of attention paid to biotech products is expected to increase sharply. We are already seeing some signs of a shift. In the past, many biotech drugs were included in medical benefits payment schemes that were subject to less scrutiny. Recently, relatively more are being classified as pharmacy benefit drugs, where scrutiny is higher.

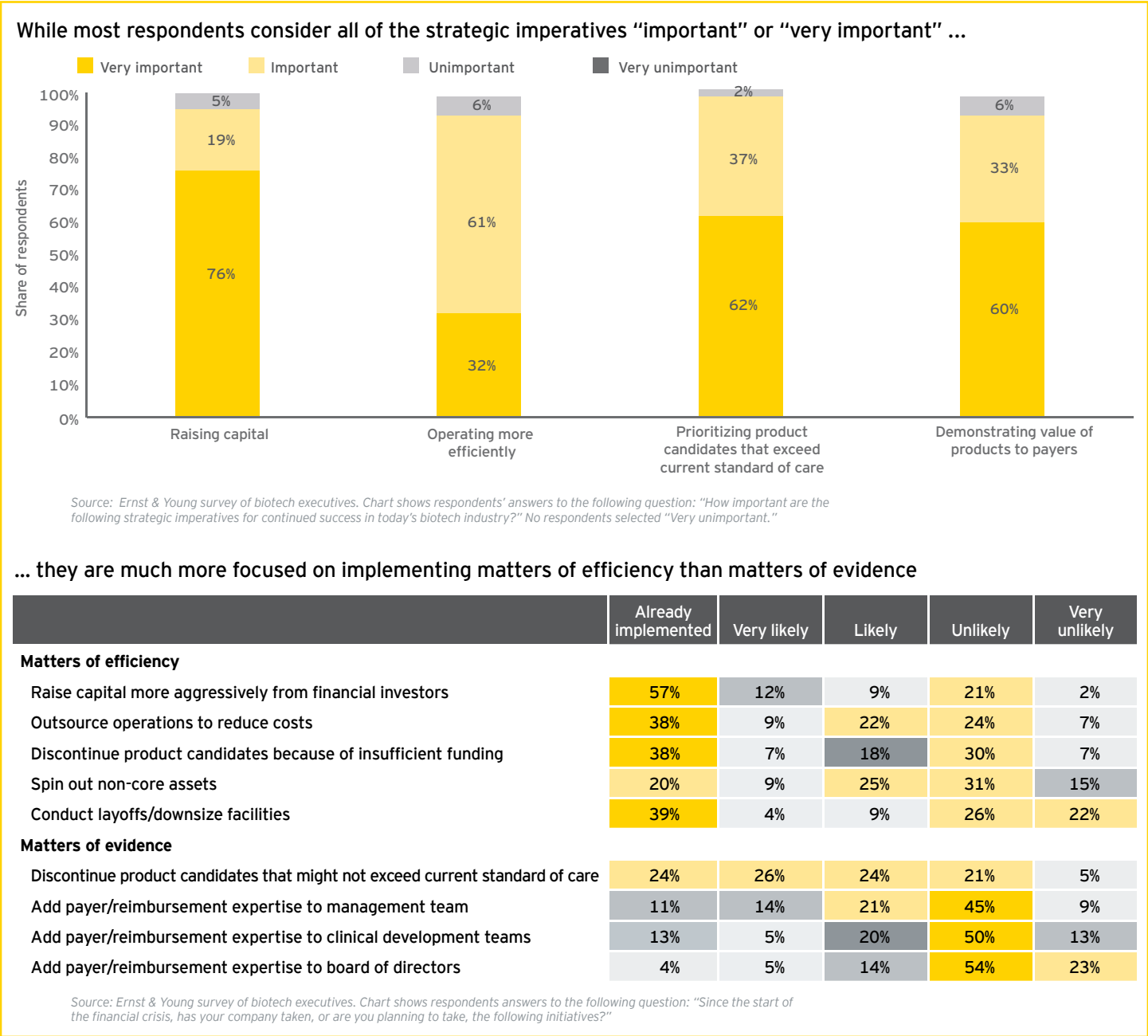
Almost five years after the start of the global financial crisis, the appropriate question is therefore not just what companies are doing to operate efficiently, but whether they are preparing adequately for the rapidly changing, evidence-driven reality of health care. By now, companies' efficiency initiatives are well established. Creative approaches to funding and conducting R&D, such as fail-fast models and asset-centric financing, are more commonplace. HOLNet-like approaches are gaining traction. But what, if anything, has changed in the ways in which biotech companies gather evidence to demonstrate the value of their products?



Matters of evidence

To explore this question, we undertook a survey of US and European biotech executives. The results, based on responses from 62 companies with revenues below US\$500 million, reveal an interesting divide between how companies are approaching matters of efficiency and matters of evidence. At the strategic

level, both sets of issues are ranked as very important for success. We asked respondents about two strategic imperatives related to the efficiency challenges of the post-financial-crisis environment (“raising capital” and “operating more efficiently”) as well as two strategic imperatives related to matters of evidence (“prioritizing



product candidates that exceed current standard of care” and “demonstrating value of products to payers”). All four strategic imperatives were rated “important” or “very important” by 94% or more of the respondents.

Almost five years after the start of the global financial crisis, the appropriate question is therefore not just what companies are doing to operate efficiently, but whether they are preparing adequately for the rapidly changing, evidence-driven reality of health care.

But when it comes to implementation, companies are much further along in enacting initiatives related to efficiency than they are on introducing measures to collect evidence and demonstrate value. For this portion of the analysis, we excluded companies that consider demonstrating value to products and payers to be “unimportant” – allowing us to focus on what specific measures are being implemented by companies that consider this an important strategic issue. With respect to matters of efficiency, the most common response was that these companies had already implemented initiatives. However, when we asked them about matters of evidence, most respondents indicated that they are unlikely to undertake specific initiatives. For instance, 57% of respondents have already raised capital more aggressively from financial investors and 39% have conducted layoffs or downsized facilities. But only 11% have added payer/reimbursement expertise to their management teams and an even smaller 4% have added such expertise to their boards.

One exception to this trend is with respect to discontinuing product candidates that might not exceed the current standard of care. Unlike the other initiatives related to matters of evidence – which most companies said they are unlikely to undertake – this is one area where half of respondents said that they had either already acted or are very likely to do so in the next one to two years. This might be a reflection of the times. In the aftermath of the financial crisis, companies have been culling their R&D programs, and it may be only natural for them to include performance versus standard of care in their exclusion criteria. It is worth noting, however, that more companies have discontinued product candidates because of insufficient funding (38%) than because of concerns that their products might not exceed the standard of care (24%).

Companies are much further along in enacting initiatives related to efficiency than they are on introducing measures to collect evidence and demonstrate value.

We supplemented the survey with interviews of a handful of venture capitalists (VCs) and business development (BD) executives from big pharma companies – key financial and strategic investors in biotech companies – to learn more about their expectations regarding data and their experiences with biotech firms in this regard. (The input from these interviews is summarized in a series of bylined text boxes that are interspersed throughout this article.)



If you build it, will it matter?



Ed Mathers

NEA

Partner

I've been in the biotechnology industry for about 30 years in a variety of capacities. Over that time, one thing has always been true: to succeed, a product needs to meet a clinical need. If it can do that, patients will benefit – and biotech companies and their investors and big pharma partners will win.

Over the last five years, however, the focus on demonstrating the economic value of product candidates has sharpened. Five years ago, if we were investing in an early-stage platform company, our primary concern would be demonstrating that the platform works and then thinking through potential applications. Today, we don't just ask, "Will it work?" We also ask, "Will it matter?" Because if a new product or platform doesn't matter to payers and pharma companies, then it is unlikely to be paid for and we are unlikely to invest in it. Nowadays, the product must not only work clinically and provide some measurable benefit relative to the standard of care, it must also offer economic advantages in terms of impacting the overall cost of therapy.

For our later-stage investments, the imperative now is to demonstrate differential economic value. Beyond efficacy, we have to be able to show that our products are differentiated relative to the standard of care (particularly in a world where generics are becoming more prevalent) and that they improve quality of life and positively affect payers.

Due diligence

In response to this transformation of the industry investing mindset, our diligence processes have been forced to adapt as well. For our early-stage investments, we don't just conduct scientific diligence – we also spend a lot of time talking to business development and commercial teams from pharmaceutical companies to ascertain whether a new product will matter to them. It is important to understand their needs and try to meet as many of them as we can.

The other area where we are doing more diligence – even prior to making early-stage investments – is in talking to private and public payers. As Medicare and Medicaid in the US adopt

bundled payment systems, for instance, it has become critical to understand at an early stage how a product would fit within a bundle. How will it make a difference, both today and over time?

With later-stage investments, our due diligence includes assessing how a new product will differentiate itself relative to the market-leading products (which could well be generic). This involves questions of clinical trial design, and it might require conducting head-to-head studies, which increases the risk of getting a result that is ambiguous or detrimental to a product's success.

For later-stage companies, it has become increasingly important to get the right kinds of expertise to address these concerns. I see a lot more activity around engaging payer consultants, talking directly to payers, etc.

Big pharma's expectations

These market differentiation issues have affected what pharma expects from biotech companies and the data packages our portfolio companies now seek to assemble. In addition to chemistry, manufacturing and control data, pharma partners also want to see what communications we have had with regulatory agencies such as the U.S. Food and Drug Administration. And they want to know what primary research we have done around the value of our product, by talking with key opinion leaders, payers and others.

In most cases, pharma companies do their own research on these value questions anyway, but it seems to help if we have spent some time and resources considering these questions as well.

Asking the right questions

For biotech companies and their investors, it is more crucial than ever to focus on demonstrating value. While early-stage companies may lack the resources – or need – to undertake head-to-head trials, it is never too early to start asking the right questions. Assuming our product works, will it matter – to patients, to payers and to health care systems at large?

Adapting to a rapidly changing environment



Denise Pollard-Knight, PhD

Phase4 Ventures

Managing Partner

Things are changing quickly in our industry. Payers are increasingly requiring evidence of health outcomes. Over the last five years or so, biotech companies and investors have therefore become more focused on demonstrating economic value – for instance, by showing survival benefit for an oncology drug or, increasingly, superiority to branded or generic competitors.

In the past, chemistry, manufacturing and control data was the area where we were most focused, but we now focus more on data related to reimbursement. Even with our earliest-stage preclinical investments, we want to understand the overall competitive landscape: payer attitudes, competing products, the size of the market, etc.

Flexibility and differentiation

Payers' needs are not the only things that can change rapidly. Even as companies conduct research and development, the standard of care is likely evolving in the background. Clinical trials therefore need to be designed flexibly, so they can adapt to changing market conditions. In oncology, for example, new therapeutics are being approved all the time – often by combining two or more medications. If you are in Phase II trials and can't add an arm to your study to incorporate a new therapeutic, your study may be out of date before it's completed. You might have to adjust to other surprises as well – some compounds might get delayed and others move faster than expected, or you might learn about products you didn't even know were in development.

Even if they are not doing a head-to-head trial, companies still need to consider how they will differentiate their products in a Phase II study. This might be done through biomarkers or other means of identifying a niche for your product (e.g., relapsed patients or a subset of patients who can't be given a therapeutic because of particular side effects). It might be achieved through flexible dosing. Or you might demonstrate lower toxicity for a new cancer drug – allowing providers to safely administer higher doses.

All of this requires different skill sets and approaches to due diligence. In addition to scientific advisory boards, we speak to lots of clinicians. We sift through what we've learned and then have a broader discussion with the board and some shareholders about what size study we can do from a finance and timing perspective. We bring together real experts for each indication and carefully thrash out clinical design protocols – especially for Phase II studies.

A key step in this process is to put yourself in the shoes of the larger company in a partnering deal and ask what differentiation the buyer or in-licenser will want to see. Because, as would be expected, pharma companies are much more focused on pricing and reimbursement and the product differentiation required to succeed. One consequence of this trend is that most mergers and acquisitions are now based on earn-outs and milestones tied to sales. Another is that the bar has been raised on what big pharma companies expect from Phase II data. If you sign a partnering deal at the end of Phase I, for example, the complexity of what you will be asked to do in Phase II is a lot more than you might have expected five years ago. If you're in oncology – or in even some other indications – identifying biomarkers has become the new standard. And so you have to start developing those biomarkers pretty early in Phase I to have them ready to go into Phase II.

Keys to success

To succeed in a rapidly changing competitive environment, companies need to keep an eye on market developments and have their wits about them. Regardless of what product you are developing or your stage of development, the key is to understand the changing standard of care, what will differentiate your offering – and what it will take to get there.

The results might be indicative of a second gap – between the efforts of biotech companies and the expectations of big pharma buyers. The interviewees were in complete agreement on the importance of gathering relevant data to demonstrate value to payers. They were all of the opinion that biotech companies need to focus on these issues and should actively consider how an ultimate product might or might not be attractive to payers. “Today, we don’t just ask, ‘Will it work?’ We also ask, ‘Will it matter?’” says Ed Mathers of NEA. “Because if a new product or platform doesn’t matter to payers and pharma companies, then it is unlikely to get paid for and we are unlikely to invest in it.”

When designing clinical trials, it is imperative for companies to collect data not just on safety and efficacy but also on how their product is differentiated relative to the current and prospective standard of care. All of this requires obtaining input from relevant experts in payer and provider organizations, as well as counsel from well-constructed boards and other advisors. “We bring together real experts for each indication and carefully thrash out clinical design protocols – especially for Phase II studies,” says Denise Pollard-Knight of Phase4 Ventures.

These preparedness gaps have real costs, all the more so at a time when IPO markets are anemic and biotech companies and their investors are looking at trade sales to larger companies as the most viable exit option.

However, while the VCs we interviewed reported that their portfolio companies are making the needed strategic and operational changes, the pharma BD executives didn’t always see things the same way. “We frequently find that the venture-backed biotech companies we encounter in deal discussions have not spent time thinking about the competitive landscape and are unprepared to differentiate their pipeline products,” says Brian Edelman of Eli Lilly and Company. Instead, Johnson & Johnson’s Tao Fu argues that “the mainstream strategy appears to be to conduct a quick study in a small indication – with an eye to demonstrating proof of principle and quickly flipping the asset to big pharma – rather than to think through how a product will perform relative to the competition and standard of care when it’s launched.”

We don’t want to overstate the significance of the “gap” between the views of VCs and BD executives. Any gap we observed is based on a very small sample of interviews. We may have had the good

fortune of selecting VCs who are particularly progressive. Or there may be a lag in play – the practices VCs and their portfolio companies have enacted recently may not become visible in deal negotiations for some time. Still, we find the comments made by pharma BD executives telling and, particularly when combined with the survey results, potentially indicative of a larger issue that needs to be addressed.

These preparedness gaps have real costs, all the more so at a time when IPO markets are anemic and biotech companies and their investors are looking at trade sales to larger companies as the most viable exit option. As Laura Levine of Merck & Co. puts it, “Alliance partners who have not prepared for demonstrating the value of their products put at risk the overall commercial viability of the acquisition target. Last-minute readjustment may be ‘too little, too late’ in a highly competitive market where timing windows are critical to commercial success.” J&J’s Fu reports that in many cases the deal will not go through until the biotech company “goes back and does a new study to generate the right kind of data – resulting in additional expense and time lost.” In other cases, the pharma company undertakes additional trials to generate relevant data, which invariably lowers the valuation the biotech firm obtains.



How differentiated is your product?



Brian Edelman

Eli Lilly and Company

*Vice President, Corporate Finance and
Investment Banking*

When we buy or partner with a venture-backed biotechnology company, we have traditionally been interested in three things: (1) the firm's intellectual property, (2) its chemistry, manufacturing and control data package and (3) its clinical data package. Over the last five years, however, we have become increasingly focused on a fourth critical item in every biotech acquisition we make: the pricing, reimbursement and access profile of the company's clinical data package.

Building such a profile involves understanding how the company's pipeline candidates are differentiated relative to the standard of care. Are they significantly safer or more effective? How do they compare to inexpensive products such as generics? For this analysis to be meaningful, however, it needs to be based not on the current standard of care as much as the prospective standard of care a few years out. This might involve a head-to-head trial with a therapy that will become generic during the time frame in which the new product might hit the market.

At Lilly, our due diligence process has evolved to become much more focused on market access and reimbursement issues. We now include senior marketing and/or market research people in the process. Each of our business units has several people who conduct business development forecasting. These forecasts are developed in close conjunction with our pricing, reimbursement, access and/or business-to-business components, so that their input is also factored into valuations.

Missing the mark

However, we frequently find that the venture-backed biotech companies we encounter in deal discussions have not spent any time thinking about the competitive landscape and are unprepared to differentiate their pipeline products. Biotech firms do best in situations where the molecule is a new mechanism of action or addresses an untreated disease – making the health economic benefit intuitively obvious. But when companies are coming into a crowded disease state where there are competing therapies, we tend to see clinical data packages that do not differentiate products relative to the standard of care.

Our due diligence often reveals that we will need to redo trials or conduct new studies on what was advertised as a commercial-decision-ready molecule. This inevitably reduces the valuations that biotech companies receive for their assets because of the additional delays and costs involved in developing the product.

Why are biotech companies so frequently unprepared to demonstrate the differentiated value of their products? I believe that underlying this development is a paradigm shift. Our society has decided that it's only willing to pay for innovation up to a point. Effectively, this translates into a situation in which only one or two agents will be reimbursed in any area of care.

The logical shakeout of this is that there will be less venture capital invested in areas where it's not intuitively obvious at the outset that a potential product could be dramatically differentiated from the standard of care. However, a lot of the substrate that is currently in the pipeline was not initiated with an appreciation for the new rules of the payer market.

Outlook

In this environment, orphan drugs will continue to be attractive. If you're developing a product in an orphan indication where there is currently no treatment, demonstrating the value of your product should be comparatively easy. Conversely, me-too products will become more risky. If you are developing the next SSRI antidepressant, your only hope of getting it reimbursed is through evidence that the product is truly differentiated – for instance, by providing better outcomes related to pain or sexual function. Making that sort of case will be very difficult.

We might lose something in the process. Lipitor, which was the seventh or ninth statin to get approved, went on to become the best-selling drug of all time, in large part because it was legitimately seen as a better treatment. In today's industry, a product like that might never get payer coverage in the first place.

Preparing for outcomes



Tao Fu

Johnson & Johnson

*Head of Mergers & Acquisitions,
Pharmaceuticals*

The need to demonstrate value to payers is becoming increasingly important. The trend started in Europe where, over the last decade or so, pricing and reimbursement have become increasingly contingent on demonstrating economic value. We are now seeing a similar shift in the US. Companies are still free to set prices in the American market, but if they can't demonstrate significant economic value, they are not going to sell a lot of product. And we only expect this scrutiny to increase over time.

These considerations are therefore becoming central to our evaluation of business development opportunities. At Johnson & Johnson, we do extensive payer research for every significant business development project we manage, particularly those that are later-stage. We certainly don't expect smaller biotech companies, with their relatively limited resources, to conduct large payer studies. But we do expect them to thoroughly think through the incremental value their products will bring to medical practice and design their clinical development plans and target product profiles accordingly.

This involves evaluating how much additional value a product might generate over the standard of care – not just for current medical practice, but also with respect to norms five or 10 years in the future, when the product is launched. This might include, for instance, identifying products that might become generic in that time frame or new market entrants with different value propositions.

Is biotech prepared?

In the deals and negotiations we enter, I find that many biotech companies are somewhat unprepared with relevant information. Many companies remain much more focused on trying to earn a quick return by choosing an indication or study that can generate data fairly easily and inexpensively. The mainstream strategy appears to be to conduct a quick study in a small indication – with an eye to demonstrating proof of principle and quickly flipping the asset to big pharma – rather than to think through how a product will perform relative to the competition and standard of care when it's launched.

Unfortunately, this strategy is unlikely to work, because it will not produce evidence aligned with what payers and big pharma buyers expect in today's market. In the deals we look at, we sometimes find that the clinical trials were not properly designed at the outset. For example, a company might conduct a Phase II trial comparing a new drug to an available marketed agent, whereas the best medical practice has already evolved to a new class of drug as the standard of care. In such cases, we cannot do a deal until the company goes back and conducts a new study to generate the right kind of data – resulting in additional expense and lost time.

Working together?

It will be important for biotech companies to find talent with the expertise to think through payer issues and design trials appropriately. However, such talent isn't easy to come by. So big pharma companies could play a role here, by working with biotech companies early in the process and giving them input on their research design. For example, at J&J, we have worked on option deals in which early-stage companies benefit from our experience in designing clinical trials while giving us an option to the program if the subsequent studies subsequently demonstrate clinical proof of concept and economic benefit.

Whether they get the expertise by attracting the right talent or by partnering with larger companies, it is absolutely critical that biotech companies focus, early, on asking the right questions and doing the killer experiments. There is little point in conducting studies or gathering data that are unpersuasive – all the more so at a time of limited resources.



Why, despite near-universal recognition of the importance of demonstrating value, are many biotech companies investing relatively little to gather the sorts of evidence that will be instrumental for their success?

Points of resistance

Why is this happening? Why, despite near-universal recognition of the importance of demonstrating value, are many biotech companies investing relatively little to gather the sorts of evidence that will be instrumental for their success? The reason appears to be that many firms do not think these trends will appreciably affect their businesses in the near term. There are several points of resistance:

Myth 1. This is only relevant for commercial-stage companies.

To some early-stage biotech companies, demonstrating value to payers may seem like a distant concern, one that will only become relevant as a product launch approaches. But our interviews with pharma BD executives and VCs demonstrate that it can have repercussions much sooner by hurting companies' ability to raise capital or obtain attractive valuations in deals. To succeed with investors, companies need to understand the standard of care, design trials appropriately and collect payer-relevant data.

Strategic and financial investors want evidence that will be compelling to payers. Are you entering negotiations with the data they want – or the data you have?

Myth 2. We can't afford this. In the post-financial-crisis business environment, companies are focused on maximizing capital efficiency. Any other activity, particularly if it is also viewed as a post-marketing issue, might seem like a non-essential diversion of resources. But even cash-strapped companies can make smart investments in demonstrating value. Designing a clinical trial differently does not have to be significantly more expensive – and it is certainly more cost-efficient than the alternative of redoing trials that failed to collect relevant data. Similarly, seeking input from key stakeholders should not require any additional expenditures.

Investing in evidence doesn't have to be expensive – and could well be a prudent use of resources. Yes, you can afford to do this. More important, can you afford not to?

Myth 3. Strong science will always get paid for. When faced with challenging circumstances, the instinctive response of many in this industry is to “stick to the knitting,” i.e., focus on developing strong science, with the assumption that meaningful scientific breakthroughs will always get paid for. This might have been good advice for weathering the funding droughts of years past, but the move to evidence-based health care is a fundamentally different

challenge. Without an understanding of treatment regimens and data to demonstrate how scientific breakthroughs improve the standard of care, reimbursement is by no means guaranteed.

Payers aren't paying for science, they are paying for value. Can you demonstrate how your breakthrough adds economic value to the system?

Myth 4. This won't affect my disease segment. Some segments, such as orphan indications or other areas of high unmet medical need, are sometimes perceived as safe havens from payer pressures. While it's true that reimbursement hurdles might be lower in such areas, no segment of the biotech industry will be substantially unaffected by these shifts. Ultimately, even in areas of high unmet need, products will have to demonstrate that the benefit they deliver justifies their cost. Rather than assuming their disease segment is a safe haven, companies would do better to understand how it is differentially affected by the shift to evidence.

Nobody is immune from these trends. Do you understand how they will affect your business?

Myth 5. These trends won't become real in the near term.

Change often comes slowly to the highly regulated world of health care, and it might seem safe to assume that the move to evidence will not become real for many years. We would argue that it is *already* becoming real. Through the ACA, the US has embarked on the biggest and boldest reform of its health care system since at least the 1960s. The signposts of change are everywhere, from the rapid headway ACOs have made in the US market to the increasing use of risk-sharing agreements in Europe. With escalating health care costs and aging populations, the pressures – and pace of change – are only expected to accelerate.

Change is coming faster than many might have expected. Are you moving forward – or assuming that time is on your side?



Guiding principles for demonstrating value

To succeed in the evidence-driven systems that are fast approaching, biotech companies – regardless of their size, segment or stage of development – will need to recalibrate R&D and commercialization based on five guiding principles:

1. **Define your value proposition.** Even at very early stages of product development, companies will need to consider questions about the value proposition of their pipeline candidates. What unique contribution could your product make to health care systems and patient outcomes? How would it affect existing treatment paradigms? Why would your offering be potentially interesting for payers? While the value proposition can be articulated and quantified more precisely as the product advances through successive phases of development, managers should still ask questions like these early on to understand why their product would be attractive for payers.

It is critical to open early lines of communication with key stakeholders and obtain input on what will, and what will not, be valued by them.

To drive behavioral change by patients, health care will become more patient-centric. We are already seeing the beginnings of this shift. New technology platforms are giving patients increased access to information and greater control over the management of their health. Meanwhile, constituents throughout the health care system – from providers to payers to life sciences companies – are attempting to better understand the behaviors, needs and preferences of patients.

This will involve engaging with key stakeholders. More than ever, companies cannot develop products under the assumption that anything that receives marketing approval will also be valued by payers, providers and patients. Instead, it is critical to open early lines of communication with key stakeholders and obtain input on what will, and what will not, be valued by them. This could involve canvassing payers, interviewing key physicians and seeking the advice of external reimbursement experts. It also means understanding the patient experience and the challenges presented by established interventions. Lastly, companies should consider adding experts with payer/reimbursement experience to their managerial leadership, R&D teams and/or boards.

2. **Understand standards of care and value pathways.** A key input for defining the value proposition will be a clear understanding of how patients are currently treated in a particular disease state, which often varies by geography within and across nations. As the VCs and BD executives we interviewed emphasized, it will be important not just to understand the standard of care today, but what the standard is expected to be *years from now*, when a product reaches the market. This requires market research to understand current treatment protocols and levels of reimbursement within the relevant disease space, identify products that will go generic by the time the product hits the market, evaluate competing products currently in other companies' development pipelines, and more.

We think a leading practice for understanding the standard of care and articulating the value proposition will be the use of the value pathway framework – a concept we introduced a couple of years ago in *Progressions*, our sister publication for the pharmaceutical industry. The value pathway for a disease is simply the set of increases or decreases in value (i.e., health outcomes) along each step of the journey that patients take. For instance, mapping the value pathway in diabetes involves identifying the different disease stages patients experience (potentially at risk, confirmed to be at risk, pre-diabetic, diabetic patient, onset of long-term complications, uncontrolled diabetes, etc.) Associated with each disease state are the interventions that form the current standard of care and increase value by improving health outcomes (e.g., screening and diagnosis, diet and exercise regimens, therapeutic interventions). There are also several “value leakages” along the pathway, or places where failures in the current system lead to reductions in health outcomes (e.g., non-adherence to treatments, lack of monitoring due to discomfort or expense).

We think a leading practice for understanding the standard of care and articulating the value proposition will be the use of the value pathway framework.

These value leakages provide an excellent starting point for biotechnology companies as they develop their strategies and decide which pipeline assets to prioritize amid growing pricing pressures and diminished resources. For instance, a company with several pipeline candidates could explore the value pathway for the diseases being targeted by each of these products.

Focusing on new endpoints



James Healy, MD, PhD
Sofinnova Ventures

General Partner

Venture capitalists have historically focused on optimizing clinical and regulatory success rates. Over the last five years, the scope of our diligence has broadened. At Sofinnova, we now increasingly include reimbursement analysis as a key component in our diligence process before making investments. We ask questions not just about how safe and efficacious a new product might be for patients, but also about whether it will lead to favorable economic outcomes for health care systems. As investors, we believe that both clinical and economic benefits are required to maximize returns.

Europe is ahead of the US in this area. As a firm that has actively invested in Europe and funded companies such as Actelion Pharmaceuticals, InterMune, Movetis and PregLem that were successful at getting product approvals in Europe, we have an informed view on how payers in key markets such as the UK, Germany and France approach these issues. The US is now moving in Europe's direction. Under the Affordable Care Act, for example, much of reimbursement is going to be pay-for-performance. Many adverse outcomes – hospital readmissions within a specified period, hospital-acquired injuries such as pressure ulcers, complications from surgeries such as catheter-associated infections and more – will no longer be reimbursed.

Adding endpoints

As part of the diligence we conduct when making an investment, we often survey broad sets of relevant physicians. More importantly, we look at how companies can demonstrate that the products being developed will benefit payer systems by decreasing the overall cost of care. This requires understanding treatment protocols – how are patients currently managed and how might a new, innovative product change that? What portion of care is currently delivered in an outpatient vs. inpatient setting? How do pharmaceuticals increase or decrease those expenses? Could a new therapy reduce surgeries, decrease hospitalizations or prevent readmissions? Measures such as these are the new data sets and endpoints that companies and investors need to focus on. Unlike clinical endpoints, they may not be required by regulatory bodies, but they are very important for increasingly influential payer systems.

Subtracting costs

A number of our portfolio companies have succeeded by focusing on clinical and economic benefit. For instance, Switzerland-based PregLem recently received approval for Esmya, a new drug for the treatment of women with fibroids. The company's Phase III studies demonstrated that, by de-bulking tumors and decreasing bleeding, Esmya may eventually help avoid or delay surgeries – thereby reducing the cost of care while also increasing patient benefit.

Meanwhile, two US portfolio companies demonstrated that their drugs have the potential to decrease hospital admissions. Hyperion Therapeutics' clinical trial in patients with hepatic encephalopathy (HE) demonstrated that patients on the active drug had significantly fewer HE events and trends, demonstrating fewer HE hospitalizations and fewer total HE hospital days. Durata Therapeutics has a long-acting, injectable antibiotic that could reduce the need to admit patients to the hospital and require less frequent home health care drug infusion.

New skills

Succeeding in this evolving landscape requires different skill sets. The best management teams understand the need to gather these payer-centric endpoints and other economic data early in a product's development. This might require them to add reimbursement experts, for example, much earlier in a company's development than they might have in the past, which could be achieved by hiring a full-time, in-house reimbursement expert or by contracting the work to specific vendors. It might also require companies to add board members that have a payer background or other expertise in the reimbursement arena.

The big picture

The US spends nearly \$2.7 trillion on health care, and pharmaceuticals represent about 10% of that total. With costs under pressure, payers will increasingly want evidence that every incremental dollar spent on pharmaceuticals generates commensurate savings in the remaining 90% of health care spending. More than ever, established and emerging drug development companies need to focus on the new endpoints – reductions in hospitalization time, lowered utilization of diagnostics, decreased outpatient visits and more – that will ultimately determine success in this changing business climate.

This mapping process allows companies to understand the current standard of care, something that the VCs and BD executives we interviewed strongly urge. But an even bigger benefit is that it highlights the leakages in value that will invariably be a key focus for payers and providers seeking cost-efficient ways to boost health outcomes. There may be ways to further prioritize these value leakages. For instance, in the US market, the ACA has already introduced penalties for hospital readmissions within 30 days of discharge. It would be reasonable to expect, therefore, that in any disease where hospital readmissions represent a significant value leakage, payers and providers would be very receptive to a new product if it was accompanied by data showing it could significantly lower readmissions. James Healy of Sofinnova Ventures argues that such metrics are the “new endpoints” against which companies need to measure their pipeline candidates.

3. **Identify new solutions for value leakages.** Once companies have identified the biggest value leakages, they should consider how their approaches might best fill these gaps. If a major cause of value leakage is non-adherence with drug regimens, might the addition of a drug delivery technology increase adherence (e.g., through extended release or reduction of physical discomfort)? If health outcomes are not being optimized because a significant portion of patients don't respond to existing treatments, could personalized medicine approaches (e.g., identifying biomarkers and developing companion diagnostics) address this value leakage?
4. **Design relevant clinical trials.** In recent years, a key focus of biotech companies has been to seek more clarity from regulators about the sorts of data required for marketing approval. With payers becoming increasingly focused on evidence, it will be every bit as important for firms to understand what data payers want and to design clinical trials

It will be every bit as important for firms to understand what data payers want and to design clinical trials accordingly.

accordingly. This includes increased use of head-to-head trials that compare a product to competing therapies rather than to just a placebo. Conducting these head-to-head trials

might sometimes seem counterintuitive. After all, companies are essentially funding studies that could potentially find a competitor's product to be superior. But we are moving to a world in which comparative effectiveness research is becoming increasingly ubiquitous and at times virtual – conducted by payers, providers and other third parties – and drug companies will no longer have a monopoly over generating data about their products. One way or the other, your products will be involved in head-to-head studies.

In addition, there are opportunities to develop the “payer value proposition” more efficiently and effectively by using adaptive trials. This is something the FDA is actively encouraging. In adaptive trials, a study can start out with multiple arms that have patients with different phenotypes. As data emerges, arms that do not respond to the drug can be dropped, while the size of arms with responsive patients can be increased. This approach helps companies demonstrate the value of their drugs and identifies subpopulations most likely to benefit from treatment. It is also capital-efficient – it provides opportunities for course correction along the way without significantly increasing the cost of a trial, because non-responding patients are quickly culled.

5. **Defend your product after launch.** A few years ago, we observed that the finish line in product development is no longer marketing approval, but reimbursement. While this analogy effectively highlights the increased focus on payers, it doesn't do full justice to today's challenging marketplace. It would be more accurate to say *there is no finish line*, because in an environment in which payers are hungry for more cost-effective solutions, companies need to focus on demonstrating value throughout a product's life cycle. In this environment, standards of care will be constantly scrutinized and revised more frequently. It is imperative that companies monitor these evolving treatment paradigms and be part of the conversation.

In addition, the emergence of big data in health care is enabling the use of data mining by payers, providers and others, allowing them to find correlations and make decisions in real time about the circumstances in which particular drugs or interventions should or should not be used. It would be strategic for drug companies to seek ways to conduct such “value mining” themselves, e.g., by forming data-centric collaborations with providers and/or payers.

The challenge of understanding value pathways and changing standards of care is similarly about connecting dots ... and HOLNets could help bring it together in a cost-efficient manner.

The resource challenge: a role for HOLNets?

As already discussed, one reason why many pre-commercial biotechnology companies are inadequately focused on matters of evidence is the concern that they don't have the requisite resources. While we feel this perception is misplaced because many evidence-related initiatives do not involve significant expenditures, it is true that some measures – e.g., conducting market research to understand the current and prospective standard of care, mapping the value pathway for different diseases, quantifying value leakages – may require resources beyond what smaller companies can muster. In these areas, we would argue that a pre-competitive approach could be a very helpful alternative.

Instead of competing in these spaces (and wasting precious resources on duplicative efforts), companies could treat them as shared pre-competitive challenges that might be addressed through HOLNets. Since HOLNets would likely be disease-specific, it would be a natural fit to work with providers to understand (or in some cases help define) changing standards of care for that disease or map its value pathway. Furthermore, since these networks are by definition holistic, they would likely bring together a diverse

set of participants – drug companies, payers, providers, disease foundations/patients and more – all of whom could provide key information needed to answer these questions. A central promise of HOLNets is that they could transform big amounts of data into genuine “big data,” by bringing together information streams from diverse sources. The challenge of understanding value pathways and changing standards of care is similarly about connecting dots. The information is out there. It just resides in many different silos, and HOLNets could help bring it together in a cost-efficient manner.

Such efforts would be in the interests of all the parties that would need to be engaged in them. They would allow payers and providers to better understand best practices and the patient experience, something that is a critical focus in the move to evidence-based health care. They would enable patients and disease foundations to make R&D more efficient and increase the odds of new treatments or cures. And of course, they would permit drug companies to invest in demonstrating value without wasting precious resources in duplicative efforts.

Confront the points of resistance

Myth 1. This is only relevant for commercial-stage companies

Strategic and financial investors want evidence that will be compelling to payers.
Are you entering negotiations with the data they want – or the data you have?

Myth 2. We can't afford this

Investing in evidence doesn't have to be expensive – and could well be a prudent use of resources.
Yes, you can afford to do this. More important, can you afford not to?

Myth 3. Strong science will always get paid for

Payers aren't paying for science – they are paying for value.
Can you demonstrate how your breakthrough adds economic value to the system?

Myth 4. This won't affect my disease segment

Nobody is immune from these trends.
Do you understand how they will affect your business?

Myth 5. These trends won't become real in the near term

Change is coming faster than many might have expected.
Are you moving forward – or assuming that time is on your side?

Implications for innovation

What does all this mean for innovation? After all, the challenge of sustaining biotech innovation has grown more acute than ever since the onset of the global financial crisis and is now one of the biggest quandaries facing the industry's leaders, investors and policy makers. This is relevant not just because of the unprecedented strain on biotech funding, but also because macroeconomic trends such as demographic change and increasing prosperity are likely to create significant unmet needs in specific disease segments. How can health care's stakeholders ensure that the innovative efforts of biotech companies are focused on addressing society's biggest unmet medical needs?

The move to evidence-based health care is, at its core, a big change in economic incentives, and big changes inevitably produce winners and losers. Since drug development – massively expensive, fraught with risk and highly regulated – depends on the right balance of economic incentives and is sensitive to changes in these incentives, it seems only natural that the move to evidence-based health care

How can health care's stakeholders ensure that the innovative efforts of biotech companies are focused on addressing society's biggest unmet medical needs?

will produce some shifts in where drug development companies focus their innovative efforts.

One area that is a net winner because of the move to evidence and outcomes is **orphan diseases**. In recent years, these indications have become increasingly popular, and even big pharma companies – the creators of the blockbuster model – have rushed in. To a large extent, this is happening because of the shift to evidence-based health systems. With payers demanding more evidence of the value products deliver, orphan diseases with relatively few existing treatments are perceived to be a safe haven.

So far, payers have been willing to pay high price tags in orphan indications because there was nothing else available and the number of patients was so small that the overall impact on their budgets was negligible. But this model is not sustainable indefinitely. Over

Embrace the new guiding principles

Principle 1. Define your value proposition

- ▶ Even in early development, seek to understand your product's contribution and why payers would value it
- ▶ Solicit input from key stakeholders
- ▶ Refine your value proposition as your product moves through phases of development

Principle 2. Understand standards of care and value pathways

- ▶ Understand the current and future standards of care
- ▶ Map value pathways for individual diseases and understand the biggest causes of value leakage
- ▶ Prioritize value leakages that payers most care about

Principle 3. Identify new solutions for value leakages

- ▶ Use approaches such as drug delivery technologies and personalized medicine to fill value leakages

Principle 4. Design relevant clinical trials

- ▶ Consider head-to-head trials to influence comparative effectiveness research
- ▶ Consider adaptive trials to identify responding subpopulations while using capital efficiently

Principle 5. Defend your product after launch

- ▶ There is no finish line
- ▶ Monitor evolving standards of care and be part of the conversation
- ▶ Explore ways to conduct “value mining” by partnering with others

time, as companies adopt personalized medicine approaches, more and more diseases will become small-population conditions. This is most visible in **oncology**, where personalized medicine approaches have made the most headway. It is striking that a number of 2012 FDA product approvals that had orphan designation are for types of leukemia. (For more details, refer to the *Products and pipeline* article in this report.) Orphan indications have seemed like a sure thing as long as they have been the exception rather than the rule. But at some point, if personalized medicine approaches become mainstream – as many analysts expect – it is worth asking whether the level of scrutiny from payers would not increase significantly. And with more and more blockbuster drugs going generic, orphan drug costs will become a larger share of payers' total drug bill, making them more visible.

On the other hand, some of the biggest challenges we face as a society are in **major chronic diseases**, which affect many more patients and, thanks to aging populations and increasingly sedentary lifestyles, are by far the biggest drivers of health care costs. If this is where the costs are, it follows that payers will be very interested in new products that can significantly lower chronic disease costs. Yet some chronic diseases, such as cardiovascular indications, have become less attractive as blockbuster drugs in these segments have gone generic. The perception is that the bar will now be raised for new products in these categories, which will have to compete against generic, inexpensive versions of entrenched and proven blockbuster products such as statins.

But, as Richard Pops of Alkermes points out in his article, there are still huge opportunities in the area of chronic diseases. One approach, which is favored by his company, is to find value leakages in these diseases and seek to address them with new solutions. For instance, Alkermes is using extended-release drug delivery mechanisms to address the significant value leakages created by non-compliance in chronic indications such as substance addiction and schizophrenia.

Another approach to chronic disease innovation at a time of heightened payer scrutiny is personalized medicine. For instance, while statins are well entrenched and widely prescribed, they are in fact relatively blunt instruments that simply do not work on a significant portion of patients – a phenomenon known as statin resistance. Targeted therapeutic versions of these drugs could therefore save health systems billions of dollars. However, companies have little incentive to identify a biomarker and develop a companion diagnostic for a drug that has already gone generic. Payers, regulators and policy makers might want to explore options for aligning incentives more appropriately in this area.

While chronic conditions such as diabetes and cardiovascular indications have large numbers of existing therapies, others, such as the **neurodegenerative diseases** Alzheimer's and Parkinson's, have a paucity of treatment options. These indications are very attractive from an economic perspective but challenging from a scientific viewpoint, because they are not as well understood. As already discussed, HOLNets can play a key role in addressing the shared scientific challenges in these diseases and helping to jump-start innovation. Indeed, it's encouraging to see that efforts based on open innovation and pre-competitive collaboration are gaining the greatest traction in neurodegenerative diseases. In his article, Hussein Manji of Janssen Research & Development (a Johnson & Johnson company) points to several such examples in which his organization is actively engaged.

Core values, core strengths

The trends discussed in this article are massive, system-wide shifts with significant implications for biotech companies. Yet, in many ways, they are familiar territory for this industry, because they represent natural extensions of its core values and strengths.

The core values at the heart of biotech – the reason it has attracted top talent from big pharma and academia since its earliest days – are the motivation to address the unmet medical needs of patients and engage in cutting-edge innovation. So far, the desire to help patients has been channeled into R&D on potentially breakthrough drugs and platforms. In the new, evidence-driven world of health care, patient-centricity will also include understanding patients' journeys through value pathways and identifying their biggest unmet needs (value leakages). Innovation will be not just about products and platforms, but also about developing new solutions to address these value leakages and about entering non-traditional partnerships around data.

Adapting to this changing environment will require strengths that biotech companies already possess. Firms in this sector have always succeeded or failed based on the soundness of their data. This will still be the case going forward, only the evidence required will involve not just safety and efficacy but also demonstrating economic value against standards of care. A core strength of biotech firms – “selling their stories” to VCs and big pharma – will also be applied more broadly, as companies engage with other key stakeholders (e.g., payers and providers) to better understand and serve their needs.

Much of what you already possess – creativity, innovation, the drive to meet unmet medical needs, the skills to generate compelling data – can be harnessed to meet the significant challenges of the new world of health care. The time to act is now. ◀



Evidence determines success



Helga Rübsamen-Schaeff, PhD
AiCuris
CEO

In October 2012, AiCuris – a German company specializing in anti-infective cures – and US-based Merck & Co. announced a licensing agreement that attracted much attention in industry circles. The deal was particularly noteworthy for the size of its up-front payment – €110 million (US\$141 million) – the largest such payment in Germany and one of the five largest worldwide. *[Editor's note: for more on the Merck/AiCuris transaction and other alliances with large up-front payments, refer to the Deals section.]*

How were such terms reached at a time when big pharma companies are structuring deals with smaller up-fronts and larger milestone payments? While each deal is unique, we believe our approach could have lessons for other biotech companies in today's challenging business environment.

Our story

At AiCuris, one of our focuses was on human cytomegalovirus (HCMV), an infection that typically has no symptoms in healthy people but can be fatal for patients with weakened immune systems. When we initially sought to out-license our lead HCMV product, Letermovir, and follow-up compounds, we had positive Phase IIa data for Letermovir in a trial involving 27 organ-transplant patients. However, we soon discovered that Phase IIa data is not sufficient to attract strong deal offers, and we were dissatisfied with the initial offers we got from potential partners.

So, we decided to invest in collecting more data. This included clinical data, through a Phase IIb trial that ended up meeting all primary and secondary endpoints.

In parallel – and just as important – we conducted market research to demonstrate the economic value of our lead product Letermovir based on several factors:

- **Good positioning in a rapidly growing market.** Our research found that the HCMV market is characterized by double-digit growth and very little competition (existing drugs have safety

issues and the only other drug candidate in Phase II trials was a prodrug of an existing drug). There is a strong basis for expecting the AiCuris drugs to significantly replace existing treatments.

- **Physician uptake.** Our analysis showed that a drug with our profile would be welcomed by physicians, not only in the transplantation indication but also for other at-risk HCMV-infected patients, such as newborns. For such at-risk patients, we discovered that physicians would be willing to use the drug for prevention. Research also indicated that there is a significant number of patients who have become resistant to existing therapies and that the drug could be used to safely treat them due to Letermovir's novel mode of action.
- **Expansion potential.** Letermovir's high efficacy and safety provides an opportunity to add indications that are currently not covered by existing drugs. Our portfolio of drugs with different modes of action could also create an opportunity to combine drugs for particular indications.
- **Attractive pricing.** We found that HCMV is seen as an indication that, due to the significant unmet medical need and high costs associated with complications, should support adequate pricing.
- **Orphan status.** HCMV is widely distributed around the world but is often undiagnosed because of the absence of symptoms. So while the potential market is huge, the immediate reality we face is that of a much smaller market. We were therefore able to obtain orphan drug status on both sides of the Atlantic – an area of increasing focus for big pharma companies.

Armed with positive Phase IIb data – and, more important, market research to support the value of our pipeline – we were approached by a number of potential partners.

Takeaways

While all our circumstances may not apply to every other biotech company, our basic approach is critical. In today's market, it is very important to show partners and payers the value of the products. Evidence determines success. ◀

Different paths to value

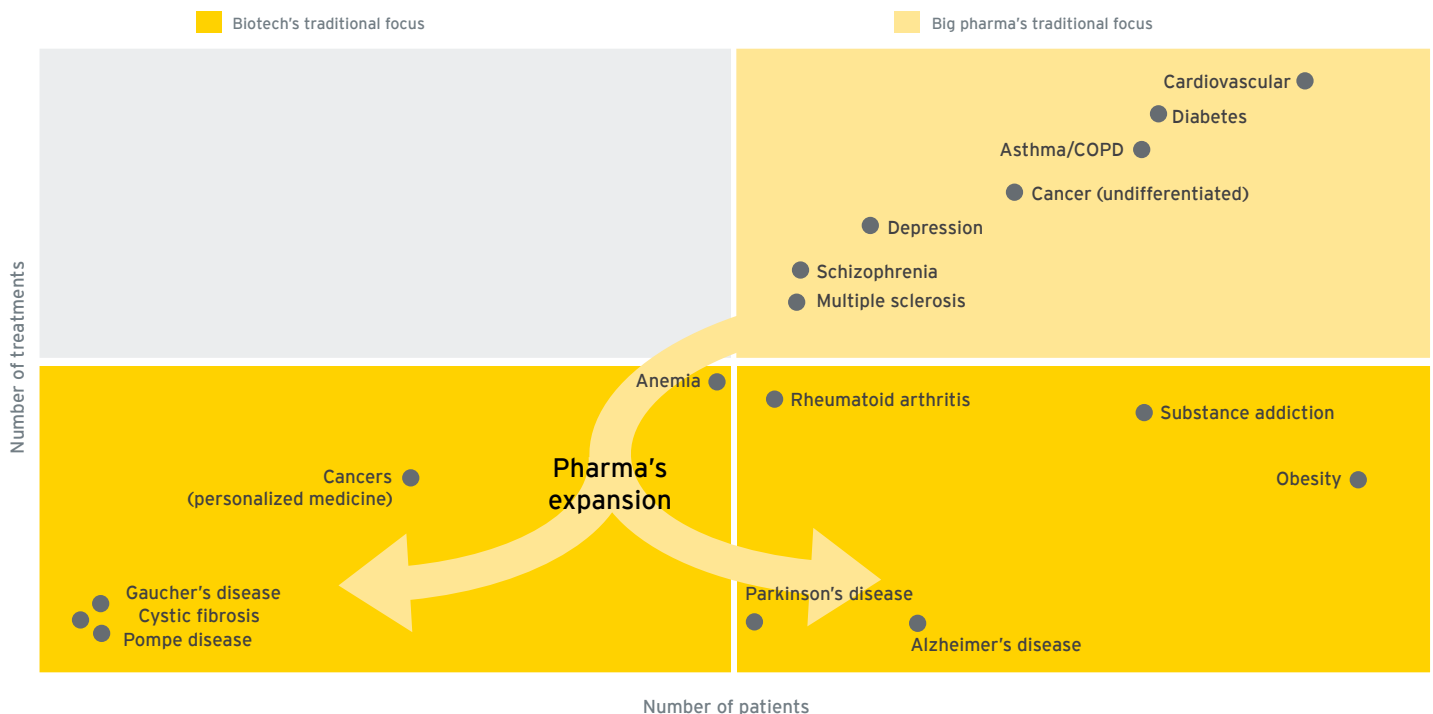


Richard Pops
Alkermes
CEO

Across drug development companies of all sizes, the simple question, “What is our most exciting new drug idea?” has been supplemented by a more nuanced one: “How can we focus on the new drug ideas that will create the most value – for patients, their families and society?” Today, the way we prioritize R&D programs, the criteria we set for selecting new product candidates and the trade-offs we make in determining their development strategies are all informed by a clear recognition of the stark realities of the reimbursement environment.

When Alkermes was getting started in the early 1990s, the situation was different. Back then, as we considered developing new drugs and dosage forms based on our innovative science, we assumed that if we could successfully complete pivotal studies, we would gain FDA approval and reimbursement. Period. The conventional wisdom was that doctors could easily use our new medicines, patients would benefit from them, and the world was as excited as we were to advance medical science in the midst of the biotechnology revolution.

Opportunities remain in chronic diseases while pharma expands into diseases with fewer treatments



Source: Alkermes, Ernst & Young. Positions of data points are approximate and intended to be suggestive of relative magnitudes.



The new standard: economics and efficacy

Today, a drug developer needs to look beyond the standard efficacy measures required for a new drug approval. Post-approval factors, most notably the reimbursement perspective, are growing in importance and are being considered up front in the drug development process. In this environment, the ideal new drugs are those for which the medical need for innovation is well aligned with the economic rationale for use.

This is not to say that an essential criterion for a new medicine should be that it saves money. Far from it – many new medicines will cost, in dollar terms, more money than the historic alternatives. But those committed to developing innovative medicines now have to expand beyond safety and efficacy measures. We have to start conceptualizing the economic rationale for our products at the earliest stages of development and then collect supporting data throughout the product development program and beyond.

Different paths to value

Biopharmaceutical companies have adapted to this profound change in the health care environment in different ways. Some companies, including many of the smaller biotechnology companies, have focused their scientific resources on brand new treatments for diseases that have few, if any, adequate current therapies. These diseases include orphan and ultra-orphan diseases, which affect only a small number of patients around the world. In addition, new personalized medicine approaches have enabled disease populations to be segmented by genetic mechanism, creating new orphan indications. In most cases, new drugs for these conditions have the potential to gain favorable reimbursement status and relatively high pricing as first-in-class medicines. Big pharma has paid attention and is responding by aggressive moves into this category of medicines.

Other companies, ours included, are choosing a different path by seeking to make significant advances in treating major chronic diseases. Despite the availability of multiple medicines, huge opportunities remain to create value by addressing critical unmet medical and economic needs for patients suffering from major chronic diseases. The appetite for such solutions is great because the economic cost of these diseases, affecting millions of people for many years, is breaking the back of our health care systems. In the US alone, chronic diseases are the leading causes of disability and account for 70% of all deaths, according to the Centers for Disease Control and Prevention.

Creating value in this chronic disease space requires an exquisite sensitivity to the advantages and limitations of current therapies – what they do for patients and what they cost – since new medicines may be competing against deeply entrenched treatment practices and, in some cases, inexpensive generic medicines. While this approach may sound daunting at the outset, it is an exciting place to focus the powerful science residing in biotechnology companies. In our case, we see major opportunities to make real advances in the treatment of important chronic diseases such as schizophrenia, addiction, depression and diabetes.

Multiple strategies, one goal

Across the full spectrum of disease – from ultra orphan to chronic – there are many places for us to apply the power of scientific innovation to create valuable new medicines. While the business of developing drugs has certainly become harder and more complex, the potential value of our innovations, for patients and for society, has never been greater. At Alkermes, we count ourselves among the biopharmaceutical companies motivated to have a profound, positive impact on the lives of large numbers of patients suffering from chronic diseases while, at the same time, taking into account the potential benefits to the health care system as a whole. ◀

Patient-centric innovation



Hussein Manji, MD

*Janssen Research & Development
A Johnson & Johnson Pharmaceutical Company*

Global Therapeutic Head for Neuroscience

The challenge of brain diseases

Brain disorders are among the most devastating ailments affecting society – something we are increasingly starting to appreciate. On one end of the age spectrum, neurodegenerative diseases such as Alzheimer's diminish and ultimately destroy lives of older people, disrupt families and threaten to bankrupt health care systems. In our rapidly aging population, the number of Alzheimer's patients is predicted to triple or quadruple by 2050, and costs could increase to over US\$1 trillion in the US alone. Today, Alzheimer's is 100% incurable, 100% fatal and 100% of patients require some sort of full-time care. To change that, we need to move from just treating symptoms to actually slowing disease progression.

At the other end of the age spectrum are serious mental illnesses. These diseases are very disabling and costly because they often emerge early in life – among adolescents or young adults – but are lifelong. They have a hugely disproportionate impact on individuals' productivity, which is increasingly important in today's knowledge-driven economy. Last year, a World Economic Forum report found that mental illnesses are projected to cost society more than cancer, diabetes and chronic respiratory diseases combined. Severe depression is predicted to be the number one cause of disability worldwide by the year 2030. In the US, it's estimated that there are more than 35,000 deaths a year from suicide, which means that there are only three forms of cancer which have a higher annual death rate.

Tackling these diseases presents some significant challenges. The brain is both the most complex and the most inaccessible human organ. As a result, the understanding of molecular brain networks is considered to be more challenging than what's required for other diseases. Our diagnostic classification is often based on signs and symptoms that aren't directly linked to a molecular path or physiology. For example, it's much easier to induce cancer in a mouse than to induce psychotic symptoms or the learning and memory problems of Alzheimer's. Our translational models need deeper scientific exploration and greater refinement.

As with a lot of R&D, neuroscience is highly specialized and can be siloed, and it will be critical to collaborate broadly. We need good biomarkers to help us measure the progression of Alzheimer's years before it is manifested in visible symptoms – but this is not something any individual entity needs to own.

It's therefore gratifying to see people collaborating in precompetitive spaces. For instance, the Alzheimer's Disease Neuroimaging Initiative (ADNI) brings together the NIH, FDA and 15 or so companies along with various university experts to identify biomarkers that predict the progression of Alzheimer's.

Patient-centric innovation

Payers and society at large are moving toward rewarding value and improved outcomes, which will encourage the adoption of more holistic solutions. The field of neuroscience could benefit tremendously from this, because brain disorders are complex and affect everything from genes to behavior to relationships, making this an area where we are more likely to need multimodal interventions that go "beyond the pill."

To succeed in this endeavor, we have to think of innovation not just in terms of scientific breakthroughs but also in terms of patient-centric innovation. At Janssen, we have realigned to create end-to-end therapeutic areas, encompassing the entire cycle of care. Even our discovery scientists need to be aware of what payers are going to reward. We try to project how payers will regard a future product, even if it's in the earliest phases of discovery.

This drives us to concentrate on genuine unmet needs. To the extent we focus on things that are already partially addressed, we have to know from the start how we might identify the subpopulation in which a new treatment will be superior – making biomarkers inevitable. Very early in clinical trials – once we've identified dose and possible side effects – we bring in an active comparator to see how our treatment compares with the standard of care in a real-world setting.

This also involves collecting data about real-world outcomes. Increasingly, society will want evidence not just of improved symptoms at three weeks, but of getting people back to work faster or improving their ability to engage in physical activities or making them less dependent on caregivers.

So far, it hasn't always been easy to get payers to focus on longer-term, real-world measures. Organizations concentrate on the budgets for which they are responsible, and gravitate to things such as minimizing short-term hospitalization costs. In the fragmented US market, broader, longer-term measures get less traction than in European countries, where interests are typically better aligned. But things are changing, and we are going to see things shift in this direction in the US as well.

New mobile health technologies are streaming behavioral and physiological data on an unprecedented scale and will play a huge role in this outcomes-driven future. In neuroscience, this is very powerful, since it can help identify when someone is about to have a relapse or stroke. After all, patients spend only a small amount of time in a physician's office – they live in the real world. We are working on technologies that would enable the integration and interpretation of different streams of data from devices and technologies, to help us move from a paradigm of “diagnose and treat” to one of “predict and preempt.”

For instance, we are developing technologies to improve adherence. Schizophrenia is one example where going off your medication for as little as 10 days dramatically increases the likelihood of re-hospitalization. The problem is compounded by the fact that some individuals with these disorders often don't have full insight into their illness. So we've developed and now market a one-month injection for schizophrenia medication and are currently developing a three-month formulation. Moving to only four injections a year could dramatically reduce relapses caused by non-adherence.

To bring all of these solutions together, we are experimenting with integrated care models. Once again, Europe has led the way. In Germany, for instance, we have a holistic care model for schizophrenic patients. Patients receive whatever care the physician deems appropriate, regardless of whether it involves our medication or a competitor's drug. The integrated care provided includes education to facilitate adherence, family counseling, rehabilitation services and more. We have similar programs in the UK as well.

Over time, we are going to have to work together to marry these new technologies with integrated care models and streaming data to inform decision-making in real time. That's not to say that technological advances at the molecular and cellular level aren't important. They're exceedingly important. But we need to think of innovation more broadly. ◀



Financial performance



Measures that matter

The big picture

Ernst & Young has been producing annual reports on the state of the biotechnology industry for 27 years, and through most of that time, the industry has been unprofitable in the aggregate. In any given year, the earnings of the relatively small number of profitable companies were overshadowed by the net losses of the much larger pool of emerging, R&D-phase enterprises. This began to change in the early- to mid-2000s, when high double-digit revenue growth and the overall maturation of the industry began to move the sector closer to aggregate profitability. While largely symbolic, the industry's move to aggregate profitability was an indicator of its strength and stability.

All of that changed when the global financial crisis hit in late 2008. As companies reacted with extensive cost-cutting measures, the industry moved firmly into the black for the first time. Yet, there was little to celebrate in this historic achievement. Biotech had become profitable almost overnight not because of a huge uptick in product sales or the rapid maturation of scores of new leaders, but because large numbers of companies had been forced to slash costs simply in order to survive. Rather than being a sign of the industry's strength and stability, biotech's overall profitability had become a by-product of uncertainty and weakness.

After 2008, much more attention has been paid to R&D spending. In an innovation-driven sector such as biotech, R&D has always been the "measure that matters," but it was a source of concern when the sector's R&D spending fell for the first time in 2009. Two-thirds of US companies cut R&D spending that year – a complete reversal

of the prior norm, which had been that two-thirds of companies raised R&D spending in any given year.

In 2011, it looked like things were heading back to normal. In last year's *Financial performance* article, we struck a cautiously optimistic note, asking whether the industry was on the path to recovery and normalization. A year later, the answer seems to be: not yet. While biotech's financial metrics continue to be healthier than they were in the immediate aftermath of the crisis, the sector is not completely out of the woods.

Growth in established biotechnology centers, 2011-12 (US\$b)

	2012	2011	% change
Public company data			
Revenues	89.8	83.1	8%
R&D expense	25.3	24.0	5%
Net income	5.2	3.8	37%
Market capitalization	477.3	376.2	27%
Number of employees	165,190	161,560	2%
Number of companies			
Public companies	598	610	-2%

Source: Ernst & Young and company financial statement data.
Numbers may appear inconsistent because of rounding.

R&D spending by public companies in the four established biotechnology centers (the United States, Europe, Canada and Australia) grew by 5% – well below the 9% growth rate achieved in 2011. The distribution of these expenditures was more worrying than the totals. Across these major markets, R&D spending by commercial leaders remained strong, while smaller, pre-commercial entities substantially reduced the pace of growth, even after normalizing for companies that were acquired during the year.

As has often been the pattern since 2008, R&D cutbacks, combined with solid revenue growth, boosted the bottom line. In 2012, the industry's net income improved by US\$1.4 billion, to reach a new high of US\$5.2 billion.

The industry's revenues grew by 8%, a couple of percentage points below the 10% (after adjusting for large acquisitions) achieved in 2011. But once again, the really interesting story is in the numbers behind the numbers. In the US, for instance, revenue growth slowed because some companies that had grown very rapidly in 2011 saw product sales stall as new competitors entered the fray with attractive propositions such as simpler treatment regimens and lower price points.

At some level, there is nothing new in this. Biopharmaceutical companies have always faced competition from the offerings of rival firms. But in today's market, where payers and providers are much more sensitive to how much new products cost and to what degree they improve the standard of care, the level of scrutiny has grown sharply. Even after products have been launched, companies will need to monitor the payer/provider environment and gather data to defend the value propositions of their products. In today's health care system, the measures that matter are therefore not just R&D spending but the increasingly critical data and metrics that demonstrate value to payers.

The good news is that biotech continues to replenish itself even in these challenging times. In 2012, a handful of up-and-coming firms in the US and Europe grew their product revenues to enter the ranks of commercial leaders. The number of FDA approvals increased to levels not seen since the Clinton Administration. To sustain their success, however, the firms introducing these new products will need to stay focused on collecting the right kinds of evidence about the value of their offerings.

Ernst & Young survival index, 2011-12

	US		Europe		Canada	
	2012	2011	2012	2011	2012	2011
More than 5 years of cash	22%	24%	36%	27%	16%	13%
3-5 years of cash	8%	8%	6%	10%	5%	7%
2-3 years of cash	15%	11%	11%	10%	8%	9%
1-2 years of cash	21%	20%	16%	20%	18%	22%
Less than 1 year of cash	33%	37%	31%	33%	53%	48%

Source: Ernst & Young and company financial statement data.

Chart shows percentage of biotech companies with each level of cash. Numbers may appear inconsistent because of rounding.

United States

US biotechnology at a glance, 2011-12 (US\$b)

	2012	2011	% change
Public company data			
Revenues	63.7	58.8	8%
R&D expense	19.3	18.0	7%
Net income	4.5	3.3	34%
Market capitalization	360.3	278.1	30%
Number of employees	100,100	98,570	2%
Financings			
Capital raised by public companies	18.4	24.6	-25%
Number of IPOs	11	10	10%
Capital raised by private companies	4.1	4.2	-2%
Number of companies			
Public companies	316	315	0%
Private companies	1,859	1,953	-5%
Public and private companies	2,175	2,268	-4%

Source: Ernst & Young and company financial statement data.
Numbers may appear inconsistent because of rounding.

Revenues of US publicly traded biotech companies grew by 8% in 2012, down from the 12% growth seen in 2011 and the 10% increase in 2009 and 2008 (on a megadeals-adjusted basis). As might be expected, given the skewed distribution of biotech industry revenues, the results were driven by developments at a few companies. This included the loss of a few sizeable firms from the universe of US biotech companies – Amylin Pharmaceuticals and Gen-Probe were acquired by large non-biotech entities, while Jazz Pharmaceuticals relocated to Ireland – but events such as these are fairly typical in any given year.

To a greater extent, the drop in revenue growth appears to be indicative of other trends – an increasingly competitive marketplace and greater scrutiny from payers and providers. For example, Vertex Pharmaceuticals – which had seen its revenues soar in 2011 after the launch of Incivek, its blockbuster hepatitis C (HCV) drug that quickly became one of the most successful product launches in the industry's history – saw its growth rate

decline in 2012 as the market prepared for a new generation of HCV drugs.

Seattle-based Dendreon Corp. is another company whose stock had initially soared on the back of a promising product approval: its prostate cancer immunotherapy, Provenge. But sales declined in 2012, driven by competitive pressures and reimbursement challenges. Increased competition took a similar toll on sales at Momenta Pharmaceuticals. Momenta had co-developed a generic version of Lovenox in collaboration with Sandoz, but the company's share of alliance revenue declined when other generics competitors entered the market.

The US biotech sector's R&D expenditures increased by 7% – slightly below the year's top-line growth and the 2011 R&D growth rate (9%). As shown in the next chart, however, the experience of US commercial leaders was quite different from that of the rest of the industry, and R&D remains under pressure at many medium-sized and small biotech firms. In 2011, a third of biotech companies had reduced R&D spending. In 2012, that number climbed to 41%.

Meanwhile, the industry's net income increased by 34%, largely reversing the decline in net income that occurred in 2011. In addition to industry stalwarts such as Amgen, Biogen Idec and Celgene Corp., strong increases in the bottom line were posted by up-and-coming firms such as Regeneron Pharmaceuticals and Incyte Corp., on the strength of recent product approvals.

US biotechnology: commercial leaders and other companies, 2011-12 (US\$b)

	2012	2011	US\$ change	% change
Commercial leaders				
Revenues	54.0	48.0	6.0	12%
R&D expense	11.5	9.8	1.7	18%
Net income (loss)	12.1	10.0	2.0	20%
Market capitalization	271.3	190.6	80.7	42%
Number of employees	67,610	64,050	3,560	6%
Other companies				
Revenues	9.8	10.9	(1.1)	-10%
R&D expense	7.8	8.2	(0.4)	-5%
Net income (loss)	(7.6)	(6.7)	(0.9)	13%
Market capitalization	88.9	87.5	1.4	2%
Number of employees	32,490	34,520	(2,030)	-6%

Source: Ernst & Young and company financial statement data.
Numbers may appear inconsistent because of rounding.
Commercial leaders are companies with revenues in excess of US\$500 million.

The performance of US commercial leaders (companies with revenues in excess of US\$500 million) was significantly better than that of the rest of the industry. Commercial leaders grew revenues and R&D expenditures by double-digit percentages, while the rest of the industry saw declines in both metrics.

While US commercial leaders typically outperform other companies in any given year, the gap between the two segments widened relative to 2011 – yet another indicator of an industry in which large numbers of smaller companies are facing a challenging funding environment and remain in cost-cutting mode. A significant gap opened up in the area of R&D spending, where commercial leaders increased expenditures by 18% and other companies cut spending by 5% (last year, both segments had increased R&D spending on an acquisitions-adjusted basis – by 4% and 2%, respectively).

The growth rates of commercial leaders and other companies were also affected by changes in the population of the two segments. For instance, commercial leaders' R&D expenditures grew faster than revenues because companies that entered the population of commercial leaders in 2012 had a higher proportion of R&D to revenues. In an "apples-to-apples" analysis using the same population of companies in both years, commercial leaders' R&D spending kept pace with top-line growth. Similarly, the market capitalization of other companies was understated because some companies with relatively large market valuations graduated into the list of commercial leaders in 2012. On an apples-to-apples basis, the market capitalization of other companies grew by 6% instead of the 2%. However, the skewing impact of these company list changes was not enough to alter the overall trend – there is a significant gap between the performance of commercial leaders and the rest of the industry.

US commercial leaders, 2008-12

2008 13 companies	2009 13 companies	2010 16 companies	2011 16 companies	2012 16 companies
Organic growth ➡		Alexion	Alexion	Alexion
Amgen	Amgen	Amgen	Amgen	Amgen
Amylin	Amylin	Amylin	Amylin	Acquired by BMS
Biogen Idec	Biogen Idec	Biogen Idec	Biogen Idec	Biogen Idec
Organic growth ➡				Biomarin Pharmaceutical
Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories
Celgene	Celgene	Celgene	Celgene	Celgene
Cephalon	Cephalon	Cephalon	Acquired by Teva	
Organic growth ➡	Cubist	Cubist	Cubist	Cubist
Organic growth ➡		Gen-Probe	Gen-Probe	Acquired by Hologic
Genentech	Acquired by Roche			
Genzyme	Genzyme	Genzyme	Acquired by Sanofi	
Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences
IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories
Illumina	Illumina	Illumina	Illumina	Illumina
Life Technologies	Life Technologies	Life Technologies	Life Technologies	Life Technologies
Organic growth ➡				Regeneron Pharmaceuticals
Organic growth ➡			Salix Pharmaceuticals	Salix Pharmaceuticals
Sepracor	Acquired by Dainippon Sumitomo			
IPO ➡	Talecris Biotherapeutics	Talecris Biotherapeutics	Acquired by Grifols	
Organic growth ➡				The Medicines Company
Organic growth ➡		United Therapeutics	United Therapeutics	United Therapeutics
Organic growth ➡			Vertex Pharmaceuticals	Vertex Pharmaceuticals
Organic growth ➡			ViroPharma	Decline in sales

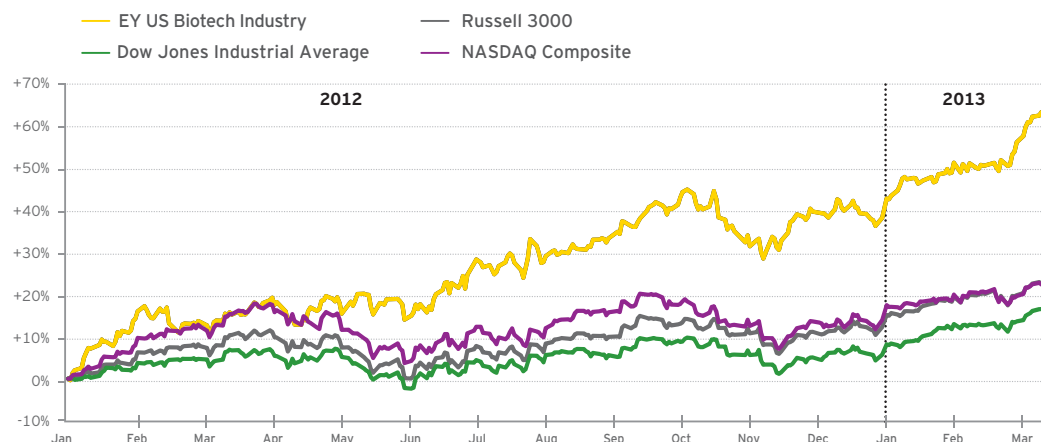
Source: Ernst & Young and company financial statement data. Commercial leaders are companies with revenues in excess of US\$500 million.

While the number of commercial leaders has held steady over the last three years at 16, the list of firms in this top tier continues to change – a reflection of the US sector's dynamism and continuous replenishment. Between 2008 and 2012, 24 US companies have been commercial leaders for at least one year, but only eight of the 24 have been on the list all five years.

In 2012, a couple of large companies – Amylin and Gen-Probe – were acquired. ViroPharma, which had just made the cut in 2011

when its revenues crossed the US\$500 million threshold, did not remain on the list in 2012 due to a decline in revenues. But the list was replenished by the emergence of other companies. Regeneron Pharmaceuticals became a commercial leader for the first time after the approval of Eylea for the treatment of macular edema, while BioMarin Pharmaceutical and The Medicines Company inched past the US\$500 million mark based on strong product sales.

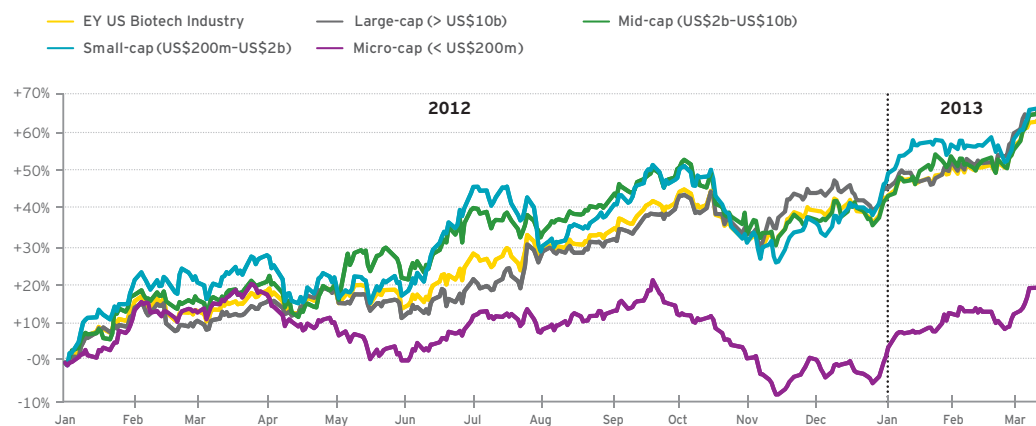
The US biotech industry far exceeded the overall market in 2012 and early 2013



Source: Ernst & Young and finance.yahoo.com.

EY US biotech industry represents the aggregate market cap of all US public biotech companies as defined by Ernst & Young.

US micro caps lagged behind the industry's stock market performance in 2012 and early 2013



Source: Ernst & Young and finance.yahoo.com.

EY US biotech industry represents the aggregate market cap of all US public biotech companies as defined by Ernst & Young.

The US stock market has been on a roll in 2012 and early 2013, with leading indices making up the ground lost since the start of the financial crisis and reaching new highs. Biotech stocks managed to do even better, with the US biotech industry outperforming the Dow, NASDAQ and Russell 3000. For the most part, companies of all sizes benefited from this trend. The only exception was micro-cap stocks, which lagged the other segments – perhaps because they had done better than every other size cohort in 2010 and 2011.

Selected US biotechnology public company financial highlights by geographic area, 2012
(US\$m, % change over 2011)

Region	Number of public companies	Market capitalization 31.12.2012	Revenue	R&D	Net income (loss)	Cash and equivalents plus short-term investments	Total assets
San Francisco Bay Area	64 -2%	95,578 59%	15,096 8%	4,664 18%	89 -93%	9,005 -45%	34,702 14%
New England	49 11%	85,654 34%	11,283 10%	4,172 22%	433 -50%	7,981 23%	21,999 18%
San Diego	33 -6%	24,348 15%	5,708 -16%	1,301 -19%	(297) -63%	3,601 -16%	14,011 -16%
New York State	28 12%	19,291 150%	2,075 78%	981 20%	487 225%	984 -20%	3,401 35%
New Jersey	22 -8%	36,861 -14%	6,329 14%	2,030 0%	1,110 21%	5,162 32%	13,541 13%
Southeast	19 -5%	2,521 -21%	206 4%	172 -14%	(203) -16%	357 -33%	709 -15%
Mid-Atlantic	17 -11%	5,180 -22%	1,480 6%	543 -33%	61 -115%	1,162 -32%	2,997 -33%
Los Angeles/Orange County	14 17%	68,242 31%	17,326 10%	3,649 9%	3,973 17%	24,250 17%	54,702 11%
Pacific Northwest	12 -14%	4,918 25%	608 21%	454 5%	(800) 12%	897 53%	1,393 83%
Pennsylvania/Delaware Valley	11 0%	4,865 -3%	1,140 22%	404 -6%	(79) -58%	318 -68%	1,342 -37%
Midwest	10 0%	1,420 53%	39 18%	220 28%	(342) 23%	413 58%	575 52%
North Carolina	9 13%	3,095 -13%	862 17%	284 -8%	(52) -318%	1,238 74%	2,390 32%
Texas	9 0%	2,239 37%	226 0%	154 2%	(144) 26%	141 -72%	394 -53%
Colorado	6 -14%	1,012 39%	85 -42%	127 -10%	(120) -30%	119 -63%	151 -61%
Utah	3 0%	2,318 25%	496 23%	59 22%	78 31%	429 -5%	784 7%
Other	10 11%	2,713 11%	776 14%	131 -3%	262 57%	592 -9%	1,208 25%
Total	316 0%	360,254 30%	63,741 8%	19,346 7%	4,466 34%	56,634 -5%	154,284 8%

Source: Ernst & Young and company financial statement data.

Percent changes refer to change over December 2011. Some numbers may appear inconsistent because of rounding.

New England: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont

Mid-Atlantic: Maryland, Virginia, District of Columbia

Southeast: Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Tennessee, South Carolina

Midwest: Illinois, Michigan, Ohio, Wisconsin

Pacific Northwest: Oregon, Washington

Europe

European biotechnology at a glance, 2011-12 (US\$m)

	2012	2011	% change
Public company data			
Revenues	20,385	18,951	8%
R&D expense	4,902	4,940	-1%
Net income (loss)	236	(19)	-1,324%
Market capitalization	79,829	71,497	12%
Number of employees	51,740	47,700	8%
Financings			
Capital raised by public companies	2,882	1,530	88%
Number of IPOs	3	8	-63%
Capital raised by private companies	1,243	1,332	-7%
Number of companies			
Public companies	165	169	-2%
Private companies	1,799	1,847	-3%
Public and private companies	1,964	2,016	-3%

Source: Ernst & Young and company financial statement data.
Numbers may appear inconsistent because of rounding.

The revenues of European publicly traded biotech companies grew by 8% in 2012 – identical to the growth rate of US companies, but slightly below the European industry's performance in 2011, when the sector's top line had increased by 10%.

However, R&D spending failed to keep pace with the top line. R&D expenditures *decreased* by 1% – an indication that many European firms are still in cost-cutting mode almost five years after the start of the global financial crisis. This is likely a reflection of European market realities – access to capital is considerably more challenging than in the US and the picture is further complicated by economic challenges and the risk of sovereign debt crises in the Eurozone.

The European biotech industry, which had reached the brink of aggregate profitability in 2011, finally crossed into the black in 2012. However, the fact that this largely symbolic milestone was reached at least in part because of widespread cost-cutting is more a source of concern than a cause for celebration.

Capital raised by European public companies soared in 2012 on the back of large debt financings by a few companies that were able to take advantage of low interest rates. (For more details, refer to the *Financing* article.)

European biotechnology: commercial leaders and other companies, 2011-12 (US\$m)

	2012	2011	US\$ change	% change
Commercial leaders				
Revenues	16,413	15,522	891	6%
R&D expense	2,726	2,641	84	3%
Net income (loss)	1,987	2,024	(36)	-2%
Market capitalization	52,787	51,667	1,120	2%
Number of employees	38,680	35,800	2,880	8%
Other companies				
Revenues	3,972	3,429	544	16%
R&D expense	2,176	2,299	(122)	-5%
Net income (loss)	(1,751)	(2,043)	292	-14%
Market capitalization	27,042	19,831	7,212	36%
Number of employees	13,060	11,900	1,160	10%

Source: Ernst & Young and company financial statement data.

Numbers may appear inconsistent because of rounding.

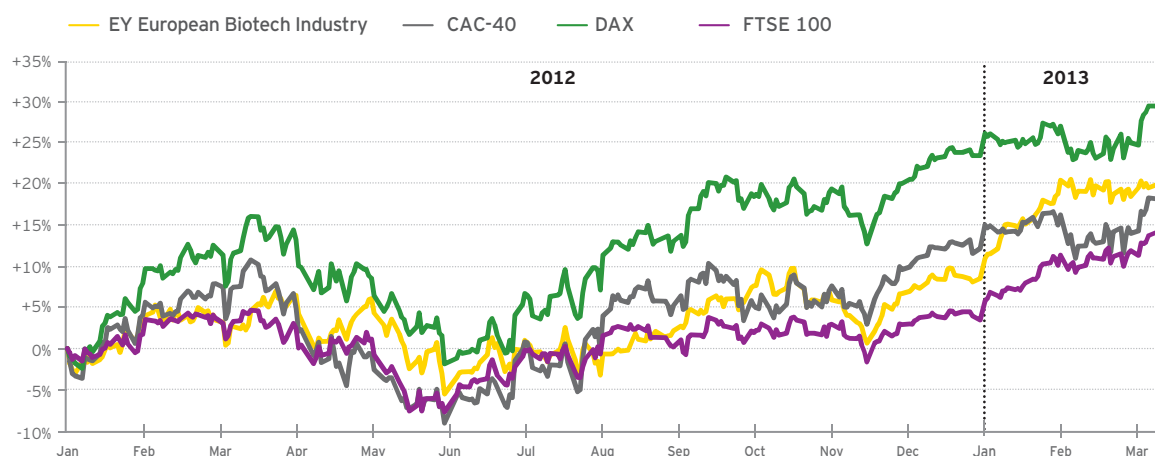
Commercial leaders are companies with revenues in excess of US\$500 million.

As in the US, the performance of biotech commercial leaders was at considerable variance with that of other companies. While the revenue growth of non-commercial leaders was faster than that of commercial leaders, the picture was reversed when it came to R&D expense, which increased by 3% at commercial leaders even as it fell by 5% at other companies – another indication that the fall in R&D was a widespread phenomenon.

As discussed earlier, the list of US commercial leaders has changed considerably over the last five years as companies lost to acquisitions have been replenished by the emergence of other fast-growing companies. In Europe, on the other hand, the list of commercial leaders remained static year after year, with just eight members: Actelion Pharmaceuticals,

Elan Corp., Eurofins Scientific, Ipsen, Meda Pharmaceuticals, Novozymes, Qiagen and Shire. In 2012, a ninth firm was added to the list, not because of organic growth at a European firm but because of the relocation of a US enterprise: Jazz Pharmaceuticals, which moved its headquarters to Ireland in connection with its merger with Azur Pharma. From Europe's perspective, the timing was excellent – Jazz had not been on the list of US commercial leaders but made the cut after relocating to Europe, thanks to the addition of Azur's revenue, the acquisition of EUSA Pharma and increased product sales. The addition of Jazz boosted the commercial-leader growth numbers shown in the accompanying chart, but not enough to change the basic trends.

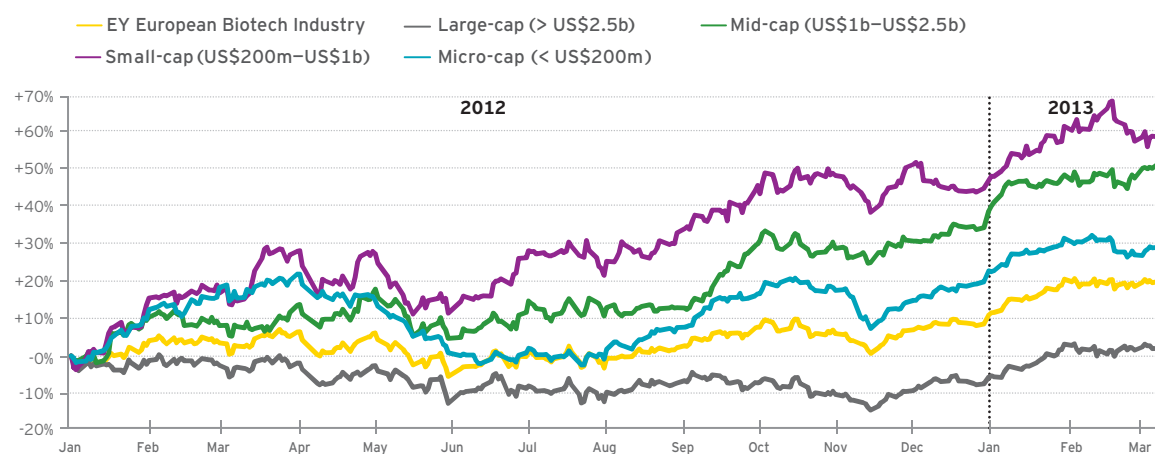
The European biotech industry performed in-line with the broader markets



Source: Ernst & Young and finance.yahoo.com.

EY European biotech industry represents the aggregate market cap of all European public biotech companies as defined by Ernst & Young.

Europe's largest biotech companies underperformed versus the rest of the industry in 2012 and early 2013



Source: Ernst & Young and finance.yahoo.com.

EY European biotech industry represents the aggregate market cap of all European public biotech companies as defined by Ernst & Young.

By the end of the first quarter of 2013, European biotech stocks were up about 20% relative to January 2012 – more or less keeping pace with the overall market. Unlike 2011, when the largest companies had outperformed the rest of the sector, these firms lagged in 2012 and early 2013.

Selected European biotechnology public company financial highlights by country, 2012 (US\$m, % change over 2011)

Country	Number of public companies	Market capitalization 31.12.2012	Revenue	R&D	Net income (loss)	Cash and equivalents plus short-term investments	Total assets
United Kingdom	31 -11%	21,344 -8%	5,470 10%	1,284 19%	570 -7%	2,205 61%	9,505 9%
Sweden	25 4%	6,247 26%	2,484 -5%	645 -5%	5 -96%	345 -21%	7,009 -10%
Israel	23 5%	2,039 27%	132 61%	113 14%	(150) -15%	298 29%	416 -8%
France	22 5%	8,178 36%	3,470 2%	583 -1%	(117) 23%	927 -21%	4,442 -15%
Germany	13 -7%	1,991 37%	265 -11%	181 -28%	(261) 69%	211 2%	914 -19%
Norway	9 0%	1,564 -1%	166 42%	50 -23%	(10) -77%	196 -11%	390 8%
Denmark	8 -11%	9,922 -8%	2,281 4%	579 9%	119 -1,099%	367 -13%	3,453 -6%
Switzerland	8 -11%	6,195 33%	1,919 -10%	621 -19%	180 -142%	1,646 -12%	3,474 -5%
Belgium	6 0%	3,578 121%	340 47%	213 -17%	(79) -62%	477 30%	854 11%
Netherlands	3 -40%	4,359 31%	1,281 8%	147 -2%	84 111%	495 70%	4,151 8%
Other	17 13%	14,411 16%	2,577 48%	485 0%	(105) -133%	1,055 21%	5,125 31%
Total	165 -2%	79,829 12%	20,385 8%	4,902 -1%	236 -1,324%	8,223 10%	39,734 1%

Source: Ernst & Young and company financial statement data.

Percent changes refer to change over December 2011. Some numbers may appear inconsistent because of rounding.

Canada

The Canadian biotech industry has been struggling since the start of the financial crisis, and 2012 brought little relief. Over the last few years, the leading Canadian companies have been acquired by foreign entities. As a result, Canada's aggregate financial results are now very sensitive to the year-to-year swings in performance that often occur at smaller firms.

In 2012, the revenues of Canadian public companies were essentially flat relative to 2011. R&D expenses, which have been on a downward trajectory for several years because of acquisitions, declined further, by 12%, in 2012, and the bottom line deteriorated by 18%.

Canadian biotechnology at a glance, 2011-12 (US\$m)

	2012	2011	% change
Public company data			
Revenues	619	612	1%
R&D expense	405	461	-12%
Net income (loss)	(303)	(368)	-18%
Market capitalization	3,763	4,103	-8%
Number of employees	2,120	2,220	-5%
Financings			
Capital raised by public companies	422	574	-26%
Number of IPOs	–	–	–
Capital raised by private companies	66	165	-60%
Number of companies			
Public companies	63	68	-7%
Private companies	154	155	-1%
Public and private companies	217	223	-3%

Source: Ernst & Young and company financial statement data.
Numbers may appear inconsistent because of rounding.

Australia

Australian biotechnology at a glance, 2011-12 (US\$m)

	2012	2011	% change
Public company data			
Revenues	5,055	4,730	7%
R&D expense	636	617	3%
Net income	777	854	-9%
Market capitalization	33,421	22,448	49%
Number of employees	11,230	13,070	-14%
Number of companies			
Public companies	54	58	-7%

Source: Ernst & Young and company financial statement data.
Numbers may appear inconsistent because of rounding.

As always, the Australian sector's performance was driven largely by CSL, which dominates Australia's biotech industry. CSL had a strong year, with robust product sales growth and net income crossing the US\$1 billion threshold for the first time.

Revenues of Australian publicly traded biotech companies grew by 7% to cross the US\$5 billion mark – slightly better than the 6% growth seen in 2011. Reflecting realities seen in the other established centers, R&D expenses failed to keep pace with the top line. While CSL recorded strong growth in both indicators, the revenues and R&D expenditures of the rest of the industry fell by 13% and 8%, respectively. Driven by its strong financial performance, CSL's market capitalization soared by more than 60% during the course of the year, while the market capitalization of the rest of the Australian sector was relatively flat, increasing by only 3%.

Financing



The same old new normal

The big picture

Since the advent of the global financial crisis in 2008, biotechnology industry funding totals have been on an upward trajectory. Despite the fact that most companies faced a challenging funding environment, capital raised increased with every subsequent year, fueled by large debt offerings by the industry's largest firms. In 2012, this trend came to an end, as capital raised in North America and Europe fell for the first time since 2008.

However, the decline was due to the same factor that had driven the sharp increases in the first place: debt. Indeed, the real story behind the numbers is one of remarkable consistency. In every year since 2008, funds raised in public equity offerings and venture capital have remained fairly steady, while large swings in the amount of debt raised have driven year-to-year fluctuations in total capital raised. While a few large companies have benefited from these funds, the amount of capital available for the vast majority of smaller, venture-backed entities has remained frozen at amounts below pre-crisis levels. This situation, which we dubbed "the new normal" in prior issues of *Beyond borders*, continued to hold in 2012.

In 2012, the amount of capital raised by biotech companies headquartered in North America or Europe dropped from US\$33.3 billion to US\$28.2 billion. This was driven almost entirely by debt funding, which fell by almost a third – from US\$20.3 billion to US\$14.1 billion.

Public offerings

Capital raised in initial public offerings (IPOs) fell slightly, from US\$857 million to US\$805 million, while funds raised in follow-on and other offerings increased by close to US\$1.5 billion, to reach US\$7.9 billion. Overall, the IPO market remains tepid in the US

and practically nonexistent in Europe, particularly relative to the era of financing "windows" that many industry participants and pundits fondly recall. While many companies filed registration statements in 2012, only 11 deals were completed in the US (one more than in 2011). Europe saw its IPO count drop by half to only three transactions in 2012 – two of which raised negligible sums. The rising stock market in the US has helped IPO aftermarket performance over the last three years, but very few generalist investors are interested in biotech IPOs. Instead, most IPO deals are bought by a concentrated group of specialist investors who can largely dictate timing and valuation.

While the IPO is the domain of the specialist investor, US follow-on public offerings attracted a more diverse set of investors buoyed by the overall strong stock market performance of the sector in 2012. Total funds invested in follow-on deals in the US increased 37% to over US\$6.6 billion, the strongest year since 2009. In all, there were 75 deals that netted proceeds of at least US\$25 million, up from 57 in the prior year. The top three deals, which netted just shy of US\$1 billion, were all by larger commercial-stage companies: Alexion, BioMarin and Amylin. The rest of the funds raised by follow-on offerings went to fund clinical development of new product candidates at smaller companies. Not surprisingly, given the budget crises and public austerity programs across the continent, follow-on offerings in Europe were not as robust and declined by about 16% to US\$948 million. Transactions above US\$25 million did increase to 13 in 2012 from 11 in the prior year, but the median deal size dropped from US\$40 million to US\$32 million.

Capital raised in North America and Europe by year (US\$m)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
IPOs	602	484	2,104	1,852	1,995	2,267	116	840	1,316	857	805
Follow-on and other	2,046	7,170	8,895	7,486	12,324	11,012	4,338	9,750	6,320	6,427	7,884
Debt	4,616	6,627	4,419	5,702	8,230	9,196	5,743	5,573	11,904	20,294	14,051
Venture	3,437	4,026	5,375	5,928	5,934	8,105	6,196	5,852	5,864	5,730	5,437
Total	10,702	18,307	20,794	20,968	28,483	30,580	16,393	22,015	25,404	33,307	28,177

Source: Ernst & Young, BioCentury, Capital IQ, Canadian Biotech News and VentureSource.
Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt."

Venture capital: waiting for the other shoe to drop

The sentiment of public investors towards biotech ebbs and flows along with broader economic trends. As a result, perhaps the most important bellwether for the health of the industry is venture capital investing. After all, the typical biotech venture investor can't reliably predict how the economy will be faring 5 to 10 years (or longer) down the line when most exits occur. Instead, his or her investment must be made on the scientific and commercial potential of a product or platform.

Since the financial crisis in particular, the conventional wisdom has been that the venture capital investing model is broken – a refrain repeated by management teams and investors alike. Indeed, several life sciences-focused firms have had to downsize their new funds or have decided to throw in the towel altogether. Others have adopted creative financing structures and models to get at some of the underlying challenges (discussed in this section as well as in prior issues of *Beyond borders*).



But despite these challenges, overall venture financing numbers have held up remarkably well since the crisis. The explanation for this apparent paradox has been that there would be a lag of a few years before the challenging venture climate would be fully reflected in fund-raising totals, because a number of funds raised capital in the “easy money” pre-crisis years, and it would take time for these funds to be invested. The expectation, therefore, has been that it is only a matter of time before “the other shoe drops” and venture funding totals fall sharply.

Yet, a full four years after the advent of the crisis, the other shoe has yet to drop. Venture funding across North America and Europe fell only slightly, declining 5% to US\$5.4 billion – but a far cry from the sharp declines that have been anticipated since the crisis first struck. Indeed, venture financing totals have held solid over the last four years, averaging about US\$5.7 billion a year.

Other indicators reveal a similar pattern of consistency. In 2012, there were 130 venture rounds in the US that had net proceeds equal to or greater than US\$10 million, with a median amount raised of US\$21 million, both essentially flat relative to 2011 (when there were 127 rounds and a median value of US\$22.5 million). In both years, these deals represented about 85% of total venture capital invested. Both years were virtually identical in terms of the number of Series A rounds that raised US\$10 million or more – a measure of new company formation. There were 25 such deals in 2012 and 27 in 2011, with a median deal size of US\$20 million-US\$25 million each year. Perhaps most encouraging, the National Venture Capital Association reports that inflows into US venture funds (across all sectors) increased by 9.7% in 2012, building on a 37% increase in 2011 from the post-crisis nadir.

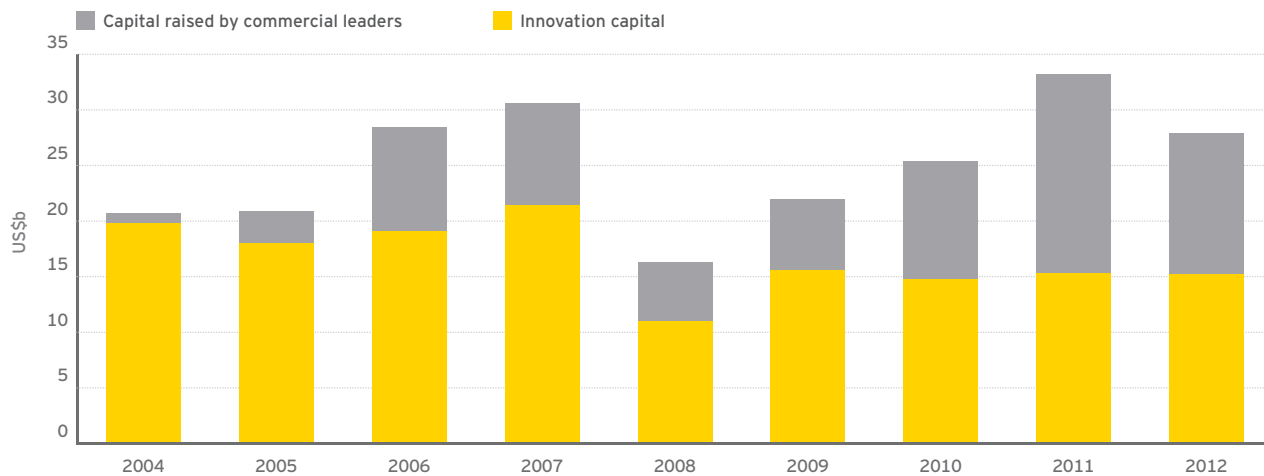
Certainly, the situation in Europe has been more challenging. Europe has a smaller pool of active venture capitalists, many of whom limit the geographic reach of their investments. This is most evident in the low number of well-funded start-ups. As in the US, the situation has stabilized – in 2012, there were 59 transactions with net proceeds equal to or greater than US\$5 million (we used a lower threshold for Europe, since average deal sizes are typically smaller) as compared to 57 in 2011. The median deal size in 2012 was just under US\$11 million, compared to US\$13 million in 2011. As in the US, Series A rounds comprised about 20% of the total, but the median Series A funding amount in 2012 was only US\$6.5 million, down from US\$12.8 million in 2011.

Innovation capital: stuck in the new normal

While the year-to-year gyrations in fund-raising amounts have been driven by a few large debt financings by mature companies, the capital available for smaller, R&D-phase companies has held steady at a significantly lower level than during the pre-crisis years. To measure this trend, we introduced a new measure a few years back: innovation capital, defined as the amount of capital raised by companies with less than US\$500 million in revenues.

In 2012, the innovation capital raised by companies in North America and Europe held steady at US\$15.3 billion, practically unchanged from the US\$15.2 billion raised in 2011. Indeed, innovation capital has been remarkably consistent over the last four years, averaging US\$15.2 billion between 2009 and 2012. However, this is considerably lower than the 2004-07 average of US\$19.6 billion. This is significant because, unlike the commercial-stage leaders, companies raising innovation capital require funding to sustain their operations and fund R&D.

Innovation capital in North America and Europe by year



Source: Ernst & Young, BioCentury, Capital IQ, Canadian Biotech News and VentureSource.
Innovation capital is the amount of equity capital raised by companies with revenues of less than US\$500 million.

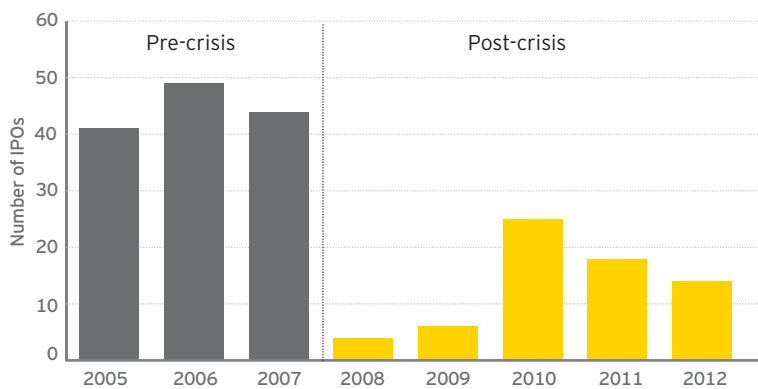


Finding an exit

In recent years, the mounting strains on the venture funding model have led to much speculation that the model is broken. Perhaps the biggest strain on the model, however, is the disconnect between the length of time to average exit of a venture-backed company as compared to the typical 10-12 year life of a venture fund. For instance, while the number of merger and acquisition (M&A) exits has held steady in recent years, the median number of years to achieve an exit has increased by 50%, from six years in 2005 to nine years in 2012.

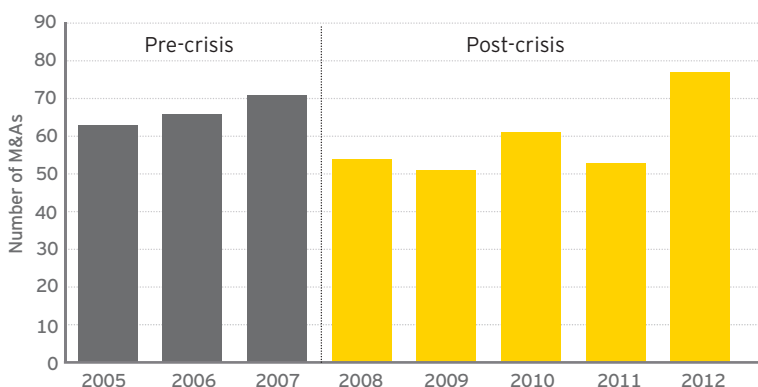
While most venture investors will continue to place long-term bets, in recent years, investors have adopted a number of strategies to enable quicker exits. These approaches remained visible in 2012. At the most basic level, investors are investing in later-stage products and management teams with commercial experience. This approach has enabled, for instance, the 2012 IPO of Massachusetts-based Tesaro a scant two years after the company's Series A financing. Another common strategy is to found a start-up jointly with a big pharma company which also takes an option to acquire the start-up following certain milestones. This was the strategy adopted by, among others, Third Rock Ventures, Greylock Partners and Sanofi, which (together with other venture investors) agreed to invest US\$125 million in Warp Drive Bio. Sanofi has an option to purchase the company in certain circumstances, and the investors also have the right to contingently put their shares to Sanofi. Finally, the asset-centric financing models we have frequently discussed on these pages fit this objective as well – even if the buyer is not necessarily known up front. Index Ventures, Versant Ventures, Atlas Ventures and others have adopted this approach of efficient development that is expected to enable quicker exits.

The number of IPOs has plummeted since the financial crisis



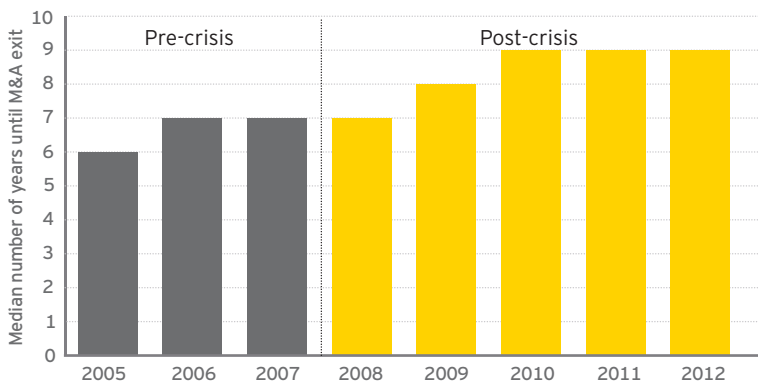
Source: Ernst & Young, Capital IQ, BioCentury, MedTRACK and VentureSource.

The number of M&A exits has held up well ...



Source: Ernst & Young, Capital IQ, MedTRACK and company news.

... but the time to M&A exit has increased



Source: Ernst & Young, Capital IQ, MedTRACK and company news.

Other people's money: big pharma competing for innovation capital

While venture investing has held firm over the last several years, new biotech start-ups are also facing competition for investor dollars from an unlikely source – big, commercial-stage companies. As a group, big pharma continues to generate billions of dollars in free cash flow and has hundreds of billions in the bank. So cash shortages are not constraining pharma's ability to invest in R&D; but budgetary pressures and investors' bottom-line expectations certainly are. As a result, we have seen a rise in creative transactions – with many more under discussion – to secure R&D funding from others, including the venture investors that typically create and invest in biotech start-ups.

These deals can be straightforward out-licensing structures or more creative "at-risk" R&D service arrangements. Examples of the former include Pfizer's out-license of four anti-inflammatory and anti-allergy drugs to Ziarco Pharma (backed by Biotechnology Value Fund) and big biotech Amgen's spin-out of Atara Biotherapeutics (backed by Kleiner Perkins Caufield & Byers). Pfizer was also active in at-risk R&D funding arrangements, having done deals with venture-backed SFJ Pharmaceuticals to fund a Phase III cancer trial in Asia and Europe, and with OxOnc (backed by OrbiMed Advisors) to fund a pivotal trial for cancer drug Xalkori in exchange for the payment of future milestones and/or royalties. In Japan, Eisai Co. has done a similar deal with SFJ, and Astellas Pharma has partnered with venture-backed Drais Pharmaceuticals on two GI tract product candidates.

United States

US biotechnology financings by year (US\$m)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
IPOs	456	448	1,565	697	1,133	1,241	6	697	1,097	814	765
Follow-on and other	1,603	4,262	6,264	5,362	7,594	5,709	3,228	7,226	4,136	4,846	6,620
Debt	4,553	6,588	4,395	5,602	7,951	8,877	5,626	4,916	11,504	19,773	11,768
Venture	1,979	2,756	3,244	3,839	3,856	5,932	4,458	4,664	4,406	4,245	4,126
Total	8,590	14,054	15,469	15,499	20,534	21,759	13,317	17,503	21,144	29,678	23,279

Source: Ernst & Young, BioCentury, Capital IQ and VentureSource.

Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt."

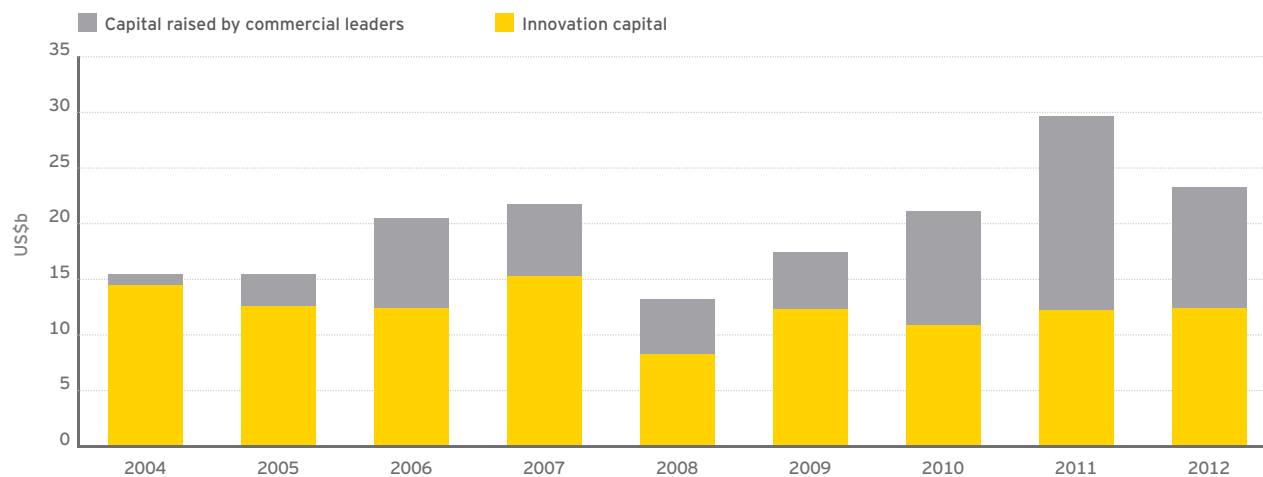
US biotechnology companies raised US\$23.3 billion in 2012 – the second-highest total over the past decade, after 2011, when the industry raised US\$29.7 billion. The fall from 2011 was driven by a decline in debt financing, from US\$19.8 billion in 2011 to US\$11.8 billion in 2012. In fact, non-debt financing increased by 16%.

Even after the decline in debt raised, the amount of debt in 2012 was the second highest over the past decade. As in prior years, Amgen (which raised US\$5 billion) and Gilead (US\$2.2 billion) were responsible for the majority of debt raised.

While venture funding and IPOs were down slightly, follow-on and other offerings were up 37%.



Innovation capital in the US by year



Source: Ernst & Young, Capital IQ, BioCentury and VentureSource.

Innovation capital is the amount of equity capital raised by companies with revenues of less than US\$500 million.

The amount of innovation capital raised by US companies was essentially unchanged from the prior year, at US\$12.4 billion. Since 2008, the industry has raised an average of US\$12 billion a year in innovation capital. Between 2004 and 2008, the average was US\$13.7 billion.

There was little seasonal variation in funding, with little quarter-to-quarter variation in funding totals across all four categories. The main exception was debt, which was significantly lower in the fourth quarter. However, significant swings are not unusual in this category, given that the numbers are dominated by a few very large transactions. Venture funding – which had started 2012 at a slow pace, with less than a billion dollars raised in each of the first two quarters – finished the year strong, but not strong enough to avoid an overall decline relative to 2011 levels.

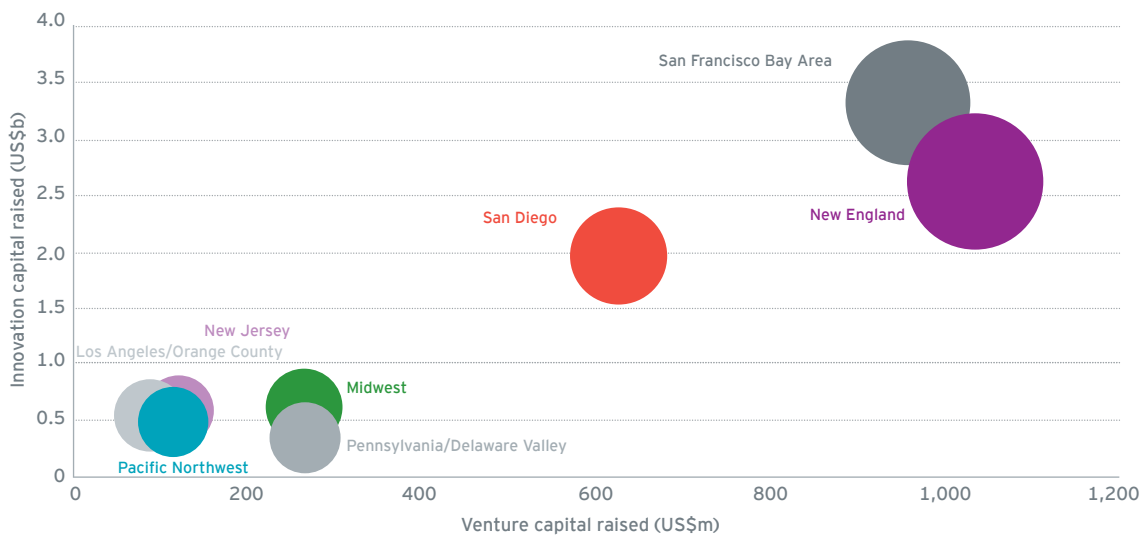
Quarterly breakdown of US biotechnology financings (US\$m), 2012

	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	\$273 (4)	\$52 (1)	\$222 (3)	\$218 (3)	\$765 (11)
Follow-on and other	\$2,283 (62)	\$1,462 (41)	\$1,504 (36)	\$1,371 (42)	\$6,620 (181)
Debt	\$3,469 (53)	\$3,496 (36)	\$4,571 (46)	\$232 (29)	\$11,768 (164)
Venture	\$982 (95)	\$772 (86)	\$1,140 (87)	\$1,231 (73)	\$4,126 (341)
Total	\$7,007 (214)	\$5,783 (164)	\$7,437 (172)	\$3,052 (147)	\$23,279 (697)

Source: Ernst & Young, BioCentury, Capital IQ and VentureSource.

Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.

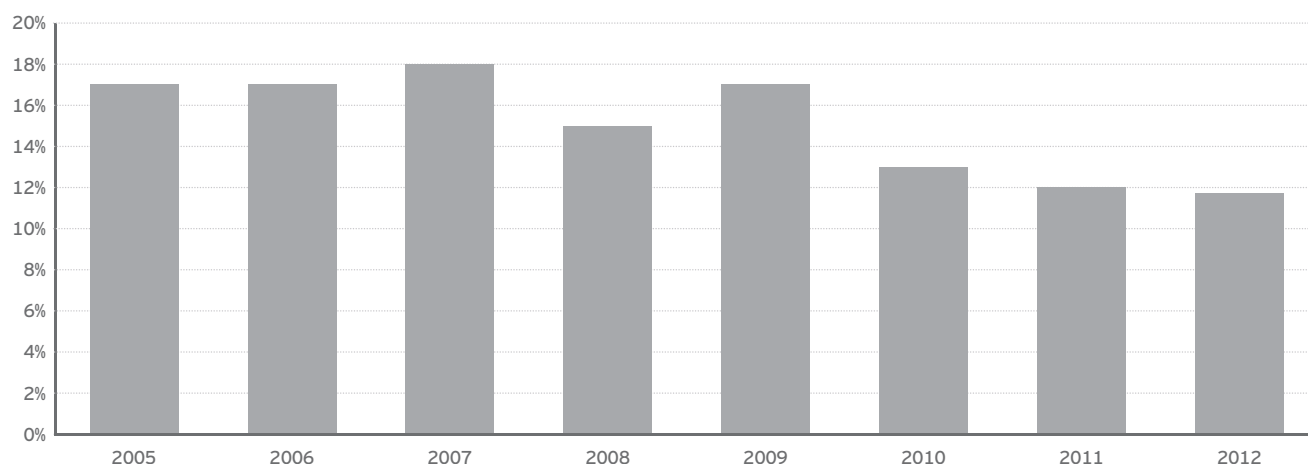
Capital raised by leading US regions, 2012



Source: Ernst & Young, Capital IQ, BioCentury and VentureSource.
Bubble sizes show relative number of financings per region. Innovation capital is the amount of equity capital raised by companies with revenues of less than US\$500 million.

As in 2011, the three leading regions for fundraising were the San Francisco Bay Area, New England and San Diego. However, in 2011, New England had led the nation in both venture capital and innovation capital raised by a wide margin. In 2012, the gap closed, with the San Francisco Bay Area inching ahead in innovation capital while New England retained the lead in venture capital. The rest of the regions are clustered together.

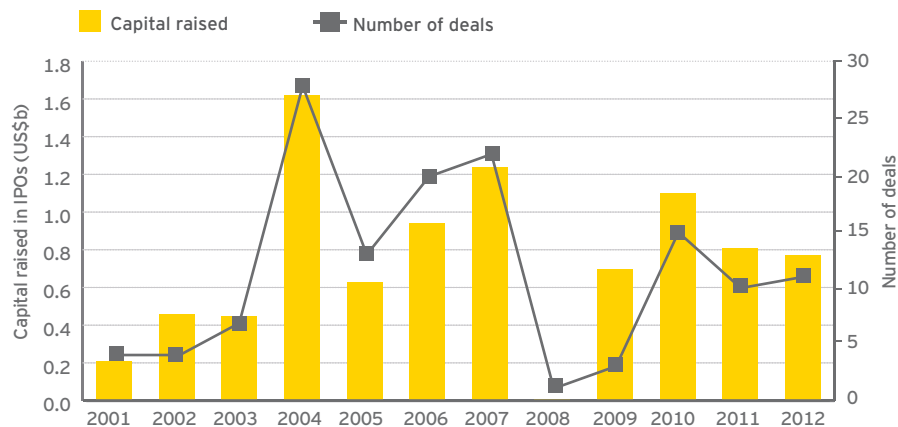
US biopharmaceutical venture capital as a share of total venture capital by year



Source: VentureSource.

The biotech industry's share of total US venture capital remained steady in 2012 at just under 12%. However, this is down quite a bit from the pre-crisis years, when the industry attracted 17%-18% of total venture funding. Meanwhile, the health care sector as a whole saw its share of total venture funding fall slightly, from 25% in 2011 to 24% in 2012.

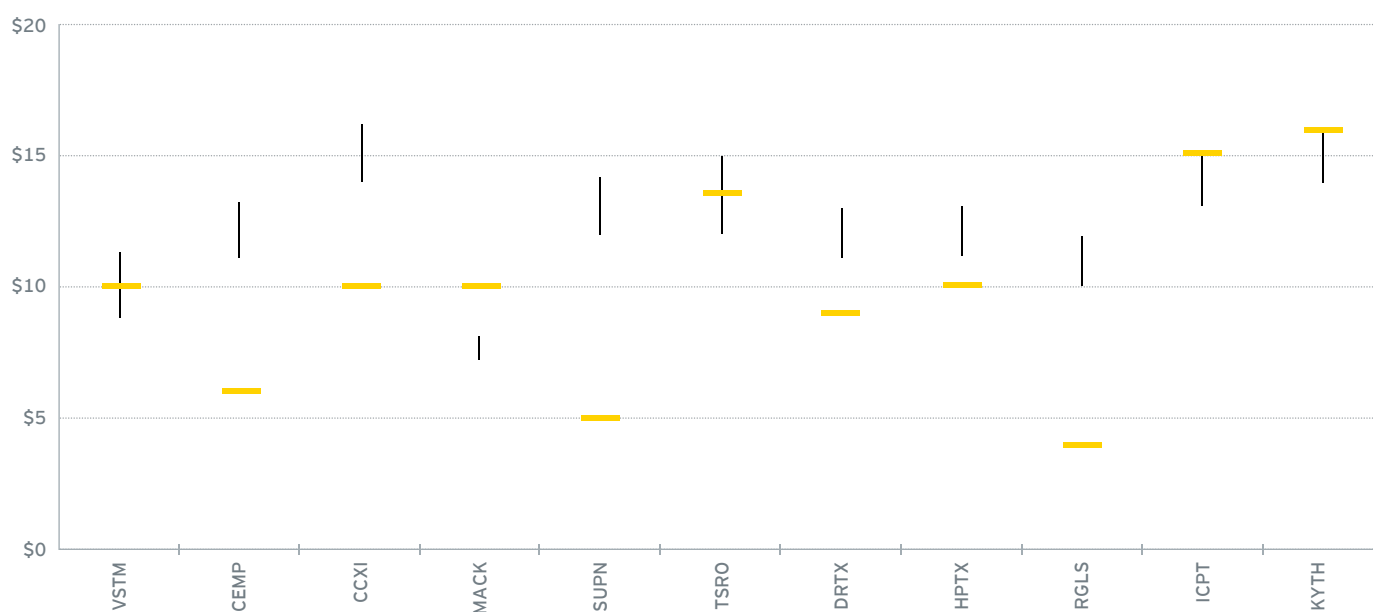
US biotechnology IPOs by year



Source: Ernst & Young, Capital IQ, BioCentury and VentureSource.

IPO activity was relatively stable compared to 2011. The number of IPOs increased slightly, from 10 to 11, while funds raised fell 6% to US\$765 million. But once again, there is a longer-term shift at play. In the four years preceding the financial crisis (2004-07) the average raised per year was US\$1.2 billion. In the four years since the crisis began (2009-12), the average has fallen by 27%, to US\$843 million.

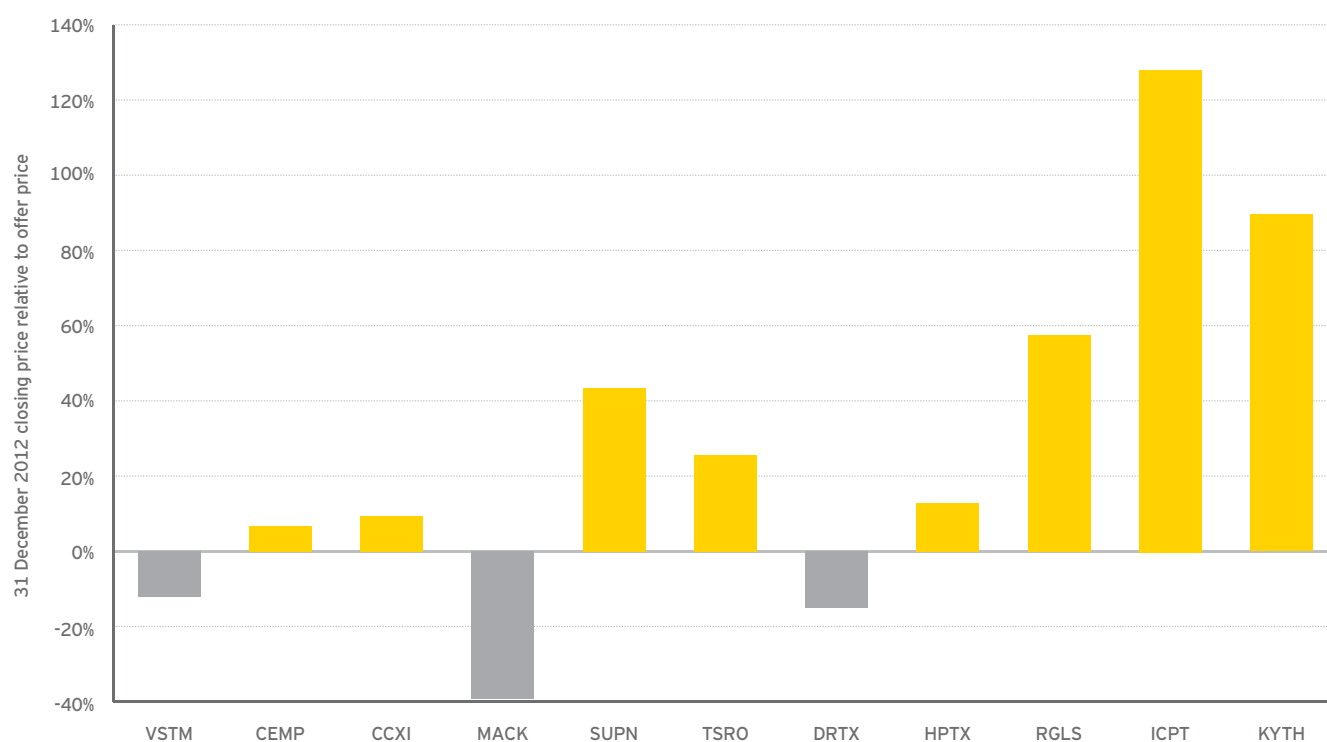
Only one company priced above its desired IPO range



Source: Ernst & Young, finance.yahoo.com and media reports.
Vertical lines indicate IPO filing ranges; horizontal dashes indicate offer prices.

In 2011, only three IPOs (30%) priced within or above their expected ranges. In 2012, that number rose somewhat to five offerings (45%). Only Merrimack Pharmaceuticals – the year’s largest IPO – priced above its desired range. However, the company’s stock was trading down by the end of the year (see next chart). All five companies that priced above or within their ranges are therapeutic companies, and three of them have products in Phase III trials.

2012 US IPO performance



Source: Ernst & Young and Capital IQ.

The year's IPOs performed much better in subsequent trading than the class of 2011 – at least somewhat because of the strength of the overall market, which has buoyed biotech stocks as well. In 2011, only 30% of companies were trading above their IPO prices by year-end. In 2012, the comparable figure

was 73%. Leading the pack was New York-based Intercept, whose primary candidate is an orphan drug for a chronic liver disease – a segment that is often perceived as attractive to payers in the current market.

Europe

European biotechnology financings by year (US\$m)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
IPOs	136	36	454	995	853	1,021	111	143	219	43	40
Follow-on and other	126	1,769	2,196	1,587	3,141	4,600	872	1,892	1,792	1,134	948
Debt	63	39	24	100	279	319	108	654	396	393	1,934
Venture	1,259	1,064	1,860	1,776	1,872	1,821	1,531	1,091	1,371	1,321	1,243
Total	1,585	2,908	4,534	4,459	6,146	7,761	2,622	3,779	3,778	2,891	4,164

Source: Ernst & Young, BioCentury, Capital IQ and VentureSource.

Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt."

While the overall numbers in Europe are a mirror image of the US performance – capital raised rose by 44% to US\$4.2 billion, the highest total since before the global financial crisis – the underlying story is not as rosy. Once again, the large year-to-year swing was entirely driven by debt financing, which increased by 392%, while every other category was down. Four European companies had debt transactions in excess of US\$150 million, including Elan Corp. (US\$600 million) and Jazz Pharmaceuticals (which relocated its headquarters from the US to Ireland in January 2012 and raised US\$575 million a few months later).

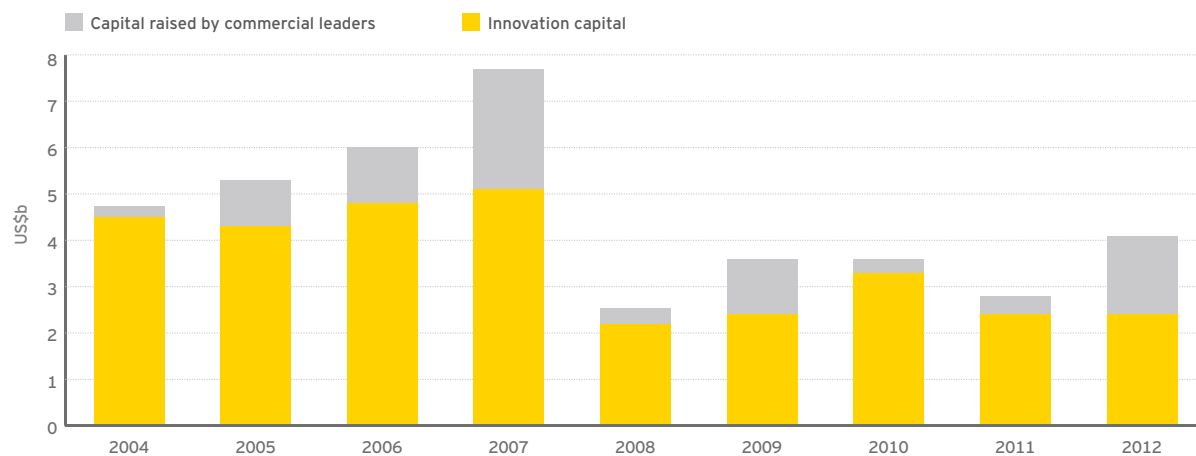
The overall picture – large debt transactions by a few commercial leaders and a challenging funding environment for most R&D-phase companies – is therefore entirely consistent

with the US situation. In fact, Europe's reality is a lot starker. IPO activity is practically nonexistent. In the four years preceding the financial crisis, the average IPO capital raised per year was US\$831 million. In the four years since the crisis, the comparable number was US\$111 million. Over the last two years, the average has fallen even further, to US\$41million – an amazing 95% decline relative to pre-crisis levels.

Venture capital has fallen from an average of US\$1.8 million raised between 2004 and 2007 to an average of US\$1.3 million in the four years since the crisis. The traditional venture financing model has essentially collapsed in Europe under the strain of several pressures: long timelines, high levels of perceived risk, management teams that often lack a proven track record, and the nonexistent IPO market discussed above.



European innovation capital by year



Source: Ernst & Young, Capital IQ, BioCentury and VentureSource.
Innovation capital is the equity capital raised by companies with revenues of less than US\$500 million.

In Europe, the majority of funding is innovation capital. However, analyzing trends in overall capital raised reveals that much of the year-to-year fluctuation has been driven by the funds raised by commercial leaders. Innovation capital for R&D at smaller companies has fallen from an annual average of US\$4.7 billion during the four years preceding the crisis to US\$2.7 billion in the four years since.

Quarterly breakdown of European biotechnology financings (US\$m), 2012

	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	\$39 (2)	\$1 (1)	\$0 (0)	\$0 (0)	\$40 (3)
Follow-on and other	\$431 (23)	\$163 (25)	\$171 (16)	\$183 (20)	\$948 (84)
Debt	\$195 (9)	\$714 (10)	\$1,023 (7)	\$2 (4)	\$1,934 (30)
Venture	\$310 (60)	\$314 (64)	\$285 (32)	\$333 (47)	\$1,243 (203)
Total	\$975 (94)	\$1,192 (100)	\$1,479 (55)	\$518 (71)	\$4,164 (320)

Venture capital held steady throughout the year. There were some fluctuations in the other categories, mostly because of a small number of transactions (IPOs) and/or the skewing effect of a few large deals (debt, follow-on and other).

Source: Ernst & Young, BioCentury, Capital IQ and VentureSource.

Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.





Capital raised by leading European countries, 2012

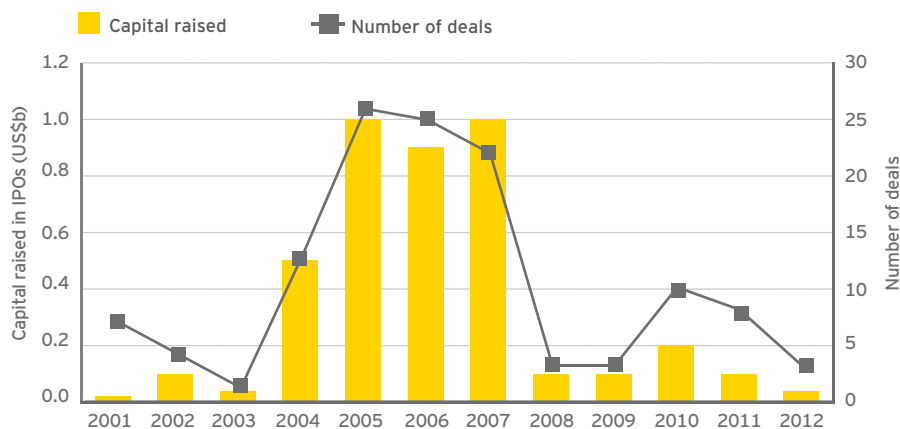


Source: Ernst & Young, Capital IQ, BioCentury and VentureSource.
Bubble sizes show relative number of financings per country.

The United Kingdom led Europe in innovation capital raised (US\$467 million) as well as the number of financing rounds. However, Germany led Europe in the amount of venture capital raised (US\$263 million), in part because of two significant financings (CureVac and BRAIN) by family offices. Other leaders included Switzerland (third-highest amount of venture capital raised) and Israel (third-highest amount of innovation capital raised).



European biotechnology IPOs by year



Source: Ernst & Young, Capital IQ, BioCentury and VentureSource.

The market for European biotech IPOs has been virtually closed since the arrival of the financial crisis and the ongoing economic challenges in the Eurozone. There were only three IPOs in Europe in 2012, which raised just US\$40 million. This was a decline even from the anemic performance in 2011, when eight IPOs raised a total of US\$43 million. Of 2012's three transactions, only one (France's Adocia, a technology company focusing on new formulations for biologics) could be considered a real IPO. The other two offerings were essentially listings that raised less than US\$5 million apiece.

On the other hand, there are some discussions ongoing which propose to biotech companies to consider floating on the stock market – even if just via listing – in order to have access to individual investors via PIPEs, gain more transparency in terms of a valuation (market cap) and avoid the even worse situation of private company financing, including the competing demands of existing venture investors and unclear market valuations.

Canada

Canadian biotechnology financings by year (US\$m)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
IPOs	10	0	85	160	9	5	0	0	0	0	0
Follow-on and other	318	1,139	435	537	1,589	703	238	633	392	447	316
Debt						0	9	3	4	127	349
Venture	199	206	271	313	205	352	207	97	87	165	68
Total	527	1,345	791	1,010	1,803	1,060	453	733	482	739	733

Source: Ernst & Young, Canadian Biotech News and company websites.

Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt". Separate subtotals for "follow-on and other" and "debt" are not available prior to 2007.

For Canada, where the financing picture has been stark since the beginning of the financial crisis, 2012 brought more of the same. For the fifth consecutive year, there were no IPOs. The amount of capital raised held steady relative to 2011, but venture funding was down by 60%. Like the US and Europe,

Canada is stuck in a funding new normal. The average amount raised in the four years prior to the financial crisis was US\$1.2 billion. In the four years since the start of the crisis, the average amount has fallen by almost half, to US\$672 million.

Quarterly breakdown of Canadian biotechnology financings (US\$m), 2012

	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	\$0 (0)	\$0 (0)	\$0 (0)	\$0 (0)	\$0 (0)
Follow-on and other	\$140 (26)	\$55 (18)	\$17 (7)	\$105 (18)	\$316 (69)
Venture	\$14 (4)	\$24 (2)	\$312 (5)	\$0 (0)	\$349 (11)
Debt	\$6 (3)	\$6 (2)	\$51 (5)	\$5 (2)	\$68 (12)
Total	\$159 (33)	\$84 (22)	\$380 (17)	\$110 (20)	\$733 (92)

Amounts raised were fairly consistent by quarter.

Source: Ernst & Young, Canadian Biotech News and company websites.
Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.



Deals



Rising demand – and selectivity

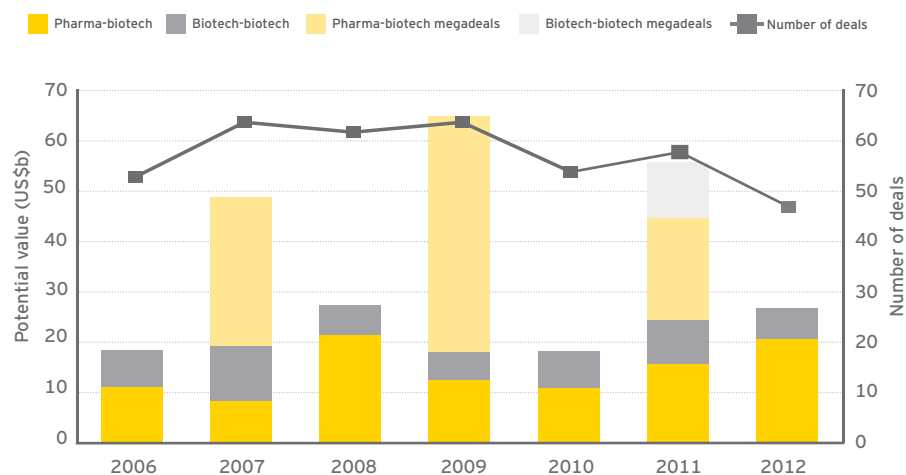
The big picture

Overall trends

In 2012, the total value of mergers and acquisitions involving US and European biotech companies increased 9% from the prior year (setting aside 2011's megamergers, which each exceeded US\$10 billion: Sanofi/Genzyme and Gilead/Pharmasset).

The US\$27.4 billion in M&A transactions announced during the year represents the highest non-megadeal total achieved since 2008. The average deal size rose to US\$566 million (the highest non-megadeal average achieved since 2005), and deal premiums for takeouts of public companies remained strong, with several in excess of 50%. However, the number of deals with disclosed deal terms declined by 19% relative to 2011.

US and European M&As, 2006-12

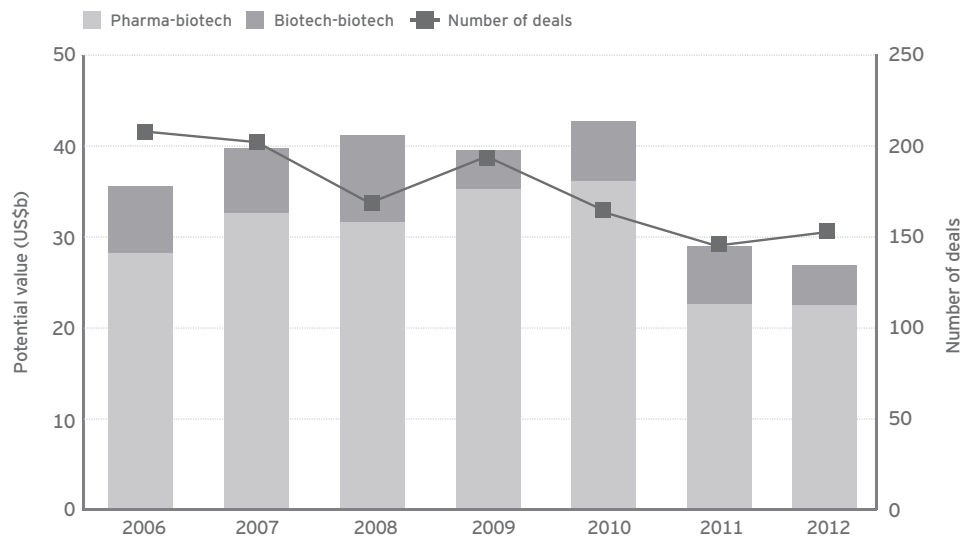


Source: Ernst & Young, Capital IQ, MedTRACK and company news.
Chart excludes transactions where deal terms were not publicly disclosed.



Meanwhile, on the strategic alliances front, the trajectory was relatively flat. In 2011, the industry had experienced a marked decrease – to the lowest levels in years – in both the volume of strategic alliances and the aggregate “biobucks” potential value of these transactions. In 2012, the number of deals increased by 4% to 153. However, their potential value fell by 9% to US\$27 billion – the lowest level in any year since at least 2005.

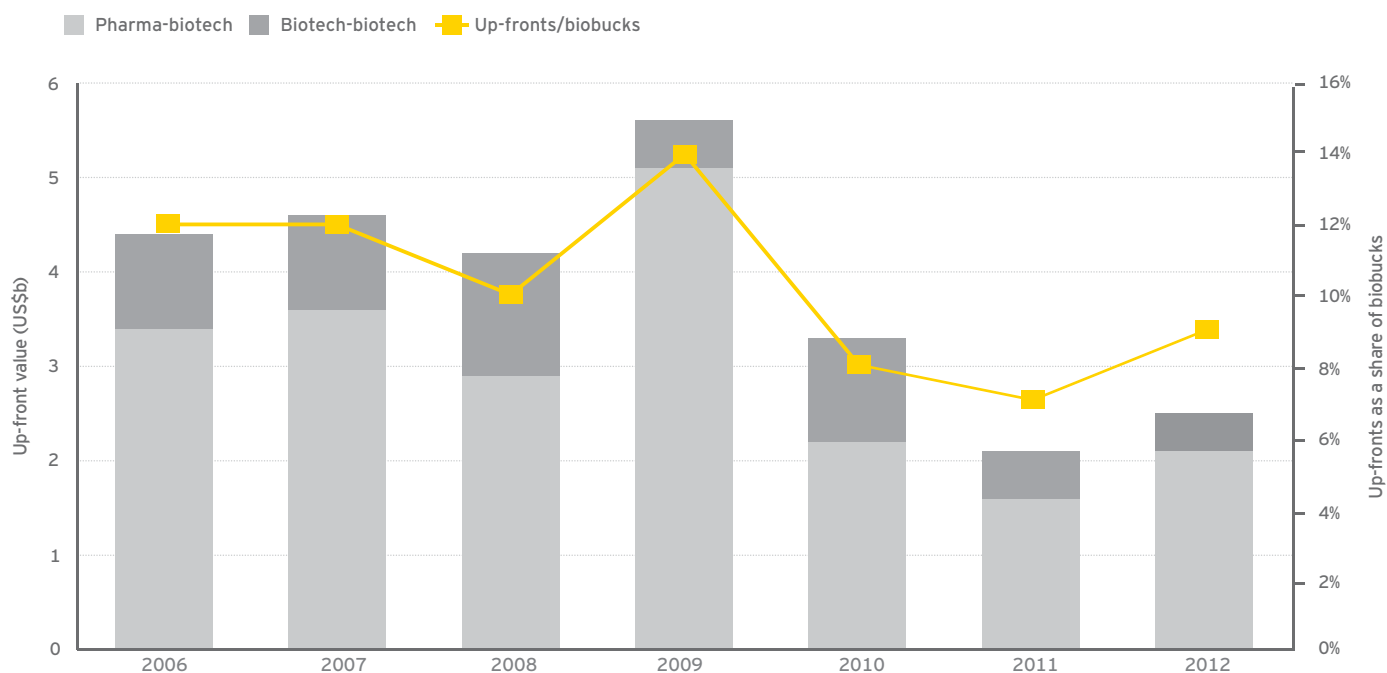
US and European strategic alliances based on biobucks, 2006-12



Source: Ernst & Young, MedTRACK and company news.
Chart shows potential value, including up-front and milestone payments, for alliances where deal terms are publicly disclosed.

What matters most to the immediate operations of biotech companies, of course, is not the potential biobucks value of alliances as much as the up-front payments included in those deals. On this front, the picture improved slightly after a steep decline in recent years. The total value of up-front payments increased from US\$2.2 billion in 2011 to US\$2.5 billion in 2012. But this was still the second-smallest total since at least 2005. Up-front payments comprised 9% of the biobucks deal value – higher than 2010-11 but still well below levels seen from 2006 to 2009.

US and European strategic alliances based on up-front payments, 2006-12



Source: Ernst & Young, MedTRACK and company news.

Larger companies, both pharma and biotech, continue to seek innovation and pipeline diversification externally. However, they also continue to be selective and price-sensitive, and this is helping keep deal values down relative to a few years ago.

Significant deals

On the M&A front, Amgen was the most active biotech buyer, nabbing Micromet, KAI Pharmaceuticals, deCODE Genetics and MN Pharmaceuticals (which sells generic injectable drugs in Turkey and surrounding countries), for an aggregate of US\$2.6 billion. Biogen Idec, Celgene and Shire also diversified their pipelines with deals that could result in aggregate payouts of up to US\$2 billion, including milestones. The largest deal of the year saw Bristol-Myers Squibb and AstraZeneca join forces (along with their diabetes franchises) to buy Amylin Pharmaceuticals for US\$5.3 billion, plus an additional US\$1.7 billion to pay Amylin's net debt and their former alliance partner Lilly (see the text box on page 61 for more on the drivers of this transaction).

The number of alliances with up-front payments in excess of US\$100 million rose from six in 2011 to eight in 2012. Abbott Laboratories, which had paid the largest up-front payment of 2011 (US\$400 million in a deal with Reata Pharmaceuticals), was very visible on this score in 2012 as well, paying large up-fronts in deals with Belgium's Galapagos and Denmark's Action Pharma.

Selected M&As by up-front payments, 2012

Company	Country	Acquired or merged company	Country	Up-front payments (US\$m)	Total potential value (US\$m)
Bristol-Myers Squibb	US	Amylin Pharmaceuticals	US	5,300	5,300
Hologic	US	Gen-Probe	US	3,800	3,800
GlaxoSmithKline	UK	Human Genome Sciences	US	3,600	3,600
Bristol-Myers Squibb	US	Inhibitex	US	2,500	2,500
AstraZeneca	UK	Ardea BioSciences	US	1,260	1,260
Amgen	US	Micromet	US	1,160	1,160
Jazz Pharmaceuticals	Ireland	EUSA Pharma	UK	680	730
Gilead Sciences	US	YM BioSciences	Canada	510	510
Bausch & Lomb	US	Ista Pharmaceuticals	US	500	500
Amgen	US	deCODE genetics	Iceland	415	415
Upsher-Smith Laboratories	US	Proximagen Group	UK	353	566
Celgene	US	Avila Therapeutics	US	350	925
Sigma-Aldrich	US	BioReliance	US	350	350
Amgen	US	KAI Pharmaceuticals	US	315	315

Source: Ernst & Young, Capital IQ, MedTRACK and company news.

"Total potential value" includes up-front, milestone and other payments from publicly available sources.

Alliances with big up-front payments, 2012

Company	Country	Partner	Country	Up-front payments (US\$m)
GlaxoSmithKline*	UK	Basilea Pharmaceutica	Switzerland	231
Abbott Laboratories	US	Galapagos	Belgium	150
Merck & Co.	US	AiCuris	Germany	141
Johnson & Johnson	US	Genmab	Denmark	135
Merck & Co.	US	Endocyte	US	120
Valeant Pharmaceuticals*	Canada	QLT	Canada	113
Abbott Laboratories*	US	Action Pharma	Denmark	110
The Medicines Company	US	Bristol-Myers Squibb	US	105
Novartis	Switzerland	ThromboGenics	Belgium	96
Celgene	US	Epizyme	US	90
Boehringer Ingelheim	Germany	Forma Therapeutics	US	65
Forest Laboratories	US	Adamas Pharmaceuticals	US	65
Allergan	US	Molecular Partners	Switzerland	63
Vidara Therapeutics*	US	InterMune	US	55
AstraZeneca	UK	Amgen	US	50

Source: Ernst & Young, MedTRACK and company news.

*Company acquired an asset from the "partner."

A bold move in diabetes



Orlan Boston
Ernst & Young

Diabetes populations are growing at an explosive rate and are on track to fuel a global crisis. With 336 million adult diabetes patients worldwide in 2011 and 10 million newly diagnosed cases annually, the economic impact in the US alone is estimated at over US\$465 billion – 11% of the nation's adult health care expenditures.

These trends create an urgent need for pharmaceutical companies to fill, and AstraZeneca (AZ) and Bristol-Myers Squibb (BMS) answered the call in 2007 by pooling their commercial diabetes assets in a global alliance centered on two products: a DPP-4 inhibitor (Onglyza/Kombiglyze XR) and an SGLT-2 inhibitor (Forxiga). But while the companies had a foothold in the market and their alliance enabled significant knowledge sharing, their diabetes pipeline prospects were still in an early stage of development, and most of their competitors were racing to enter and/or expand their diabetes franchises. As such, it was clear that AZ and BMS needed a bolder move to capture the rapid growth opportunities in this market and position the alliance as a leader in diabetes. However, both firms also face patent expirations that reduce their ability to make big investments individually.

The solution to this challenge came in the form of the largest biotech deal of 2012 and perhaps one of the most complex in recent memory, a novel acquisition involving four parties. Under the deal terms, AZ and BMS would jointly purchase Amylin Pharmaceuticals – a San Diego-based biotech company focused on diabetes – along with rights from Eli Lilly and Company to commercialize Amylin products globally. BMS served as the primary acquirer in this US\$7 billion deal (US\$5.3 billion in equity, US\$1.7 billion of assumed debt including amounts due to Lilly). AZ contributed half of this amount in cash to gain rights to half the profits from the Amylin products plus an additional US\$135 million to acquire equal governance rights related to alliance strategy and financial decisions. Structuring the deal with a single acquirer (BMS) – something that was enabled by the trust built over the years the two companies spent as alliance partners – helped accelerate its closing. The deal gives the alliance a portfolio of the three fastest-growing drug classes

in diabetes. It gives them access to the GLP-1 agonist market, including Bydureon, the world's first weekly GLP-1, and Amylin's pipeline of product extensions already under way. The transaction also generates significant operational cost synergies – estimated at 30% of R&D and SG&A expenses in 2013. By pooling resources, AZ and BMS were able to make a bold move in the market and strengthen their relationship both financially and organizationally.

But as with any transaction this large, the deal comes with complexities. The global integration of the Amylin acquisition – by far the largest in recent history for both AZ and BMS – will be jointly managed across the more than 80 markets served by the two firms. To address this challenge, the companies are collaborating more closely and have even created a joint, co-located diabetes organization within the US. The result: the companies' global diabetes alliance is stronger than ever, positioning them to grow and innovate more quickly in a rapidly growing market.

The lack of a favorable (or even predictable) IPO market in recent years has made M&A the preferred exit for venture investors. As a result, many of the year's acquisitions were of private companies, including 23 transactions in which the deal value exceeded US\$25 million. The median deal size of these transactions was US\$200 million, roughly comparable to 2011. Since acquisitions of venture-backed companies have increasingly included contingent milestone payments, it is also useful to look at cash received at closing. In 2012, there were 20 deals of greater than US\$25 million that disclosed the cash that transferred at closing, at a median amount of US\$100 million.

In strategic alliances, there was a moderate uptick in big deals. The number of deals with potential values greater than US\$1 billion doubled to six, while the number of transactions with up-front payments in excess of US\$100 million increased from three to seven. In 2012, big pharma companies Johnson & Johnson and Merck & Co. completed, respectively, eight and five deals with aggregate potential values of US\$2.5 billion and US\$2.8 billion. Among the big biotechs, Biogen Idec and Celgene each completed five deals, with potential aggregate values of US\$1.2 billion and US\$1.3 billion, respectively. Of Biogen's five alliance transactions, three were with a single partner, Isis Pharmaceuticals.

Big biobucks alliances, 2012

Company	Country	Partner	Country	Total potential value (US\$m)	Up-front payments (US\$m)
Allergan	US	Molecular Partners	Switzerland	1,463	63
Abbott Laboratories	US	Galapagos	Belgium	1,350	150
GlaxoSmithKline	UK	Five Prime Therapeutics	US	1,191	30
Johnson & Johnson	US	Genmab	Denmark	1,135	135
Les Laboratoires Servier	France	MacroGenics	US	1,100	20
Merck & Co.	US	Endocyte	US	1,000	120
Sanofi	France	Selecta Biosciences	US	900	ND
Boehringer Ingelheim	Germany	Forma Therapeutics	US	815	65
Bayer	Germany	Evotec	Germany	761	15
Johnson & Johnson	US	Forma Therapeutics	US	700	ND
Roche	US	Xenon Pharmaceuticals	Canada	646	ND
Merck KGaA	Germany	Symphogen	Denmark	636	26
Biogen Idec	US	Isis Pharmaceuticals	US	630	30
Merck & Co.	US	Ablynx	Belgium	587	11
Merck & Co.	US	AiCuris	Germany	569	141

Source: Ernst & Young, MedTRACK and company news.

"Total potential value" includes up-front, milestone and other payments from publicly available sources. "ND" refers to deals where up-front amounts were not publicly disclosed.



Shifts in firepower

As discussed, big pharma returned to the M&A scene in a significant way in 2012. The total value of pharma-biotech M&A transactions involving US or European biotech companies was US\$20.6 billion, up 32% on a non-megadeals basis from a year earlier. A key driver of this increase was pharma's growing appetite for biotech assets to compensate for the patent cliff and slower growth in emerging markets.

But even as pharma's appetite for deals has increased, its capacity to spend on assets has declined. To estimate the size of these shifts, we developed the Ernst & Young Firepower Index. Simply put, a company's firepower is diminished when its available cash and investments and market value decline, and/or when its debt level rises.

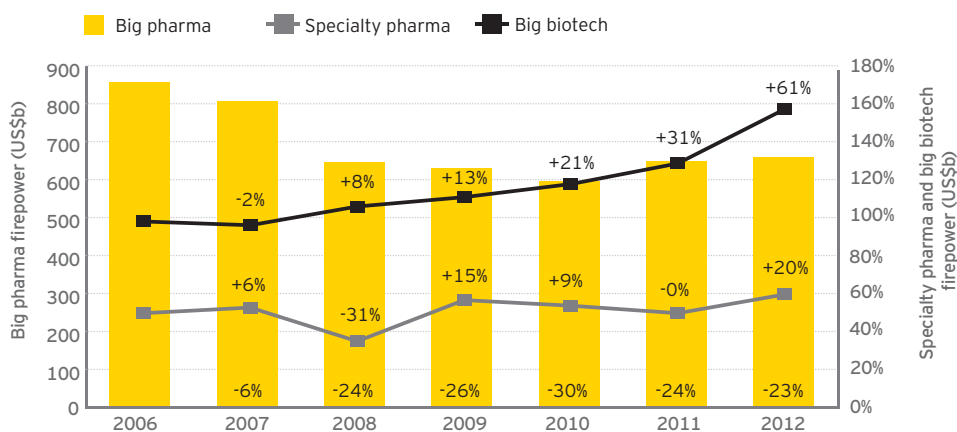
As big pharma has approached and gone over the patent cliff, its firepower has fallen markedly in recent years, primarily as a result of lower margins and increased debt. However, the next tier of companies, including big biotech companies with revenue in excess of US\$1 billion, has seen its firepower increase as a result of strong organic growth and limited generic exposure. Indeed, big pharma is the buyer in less than 20% of M&A deals. This shift in power has implications for deal-making. On the one hand, it could lead to more potential suitors for any particular transaction (favoring those companies that are nimble and retain financial flexibility), which in turn could drive higher premiums; on the other hand, big pharma may become more selective with respect to the types of companies it will pursue, in order to conserve resources.

While deal volume fell in 2012, the underlying drivers of transactions remain, and we expect to see volumes rebound to historical trends. While certain big pharma companies may be under pressure to complete a "transformational" deal, we expect to see aggregate deal values increase through more "bolt-on" transactions, with the acquirers increasingly coming from the ranks of big biotech.

On the road to exit

The time it takes for a start-up to reach sustainability has increased significantly over the history of the biotech industry, in part because the scientific and medical challenges that companies are tackling have become more complex. In 2011, Vertex Pharmaceuticals received its first FDA approvals – 22 years after the company was founded. In early 2013, ImmunoGen achieved the same feat after a remarkable 31 years. (For more on the time to exit, see the *Financing* article). While these examples are testaments to companies' perseverance, they also indicate that only a small number of biotech companies will have a shot at becoming self-sustaining independent entities. Management teams must therefore build with the long term in mind – but most investors expect to exit via an M&A transaction long before consistent profitability is achieved. Fortunately, the activities that generate long-term value – such as prioritizing the right products and demonstrating their value, as discussed in this year's *Point of view* article – are also the activities most likely to attract suitors.

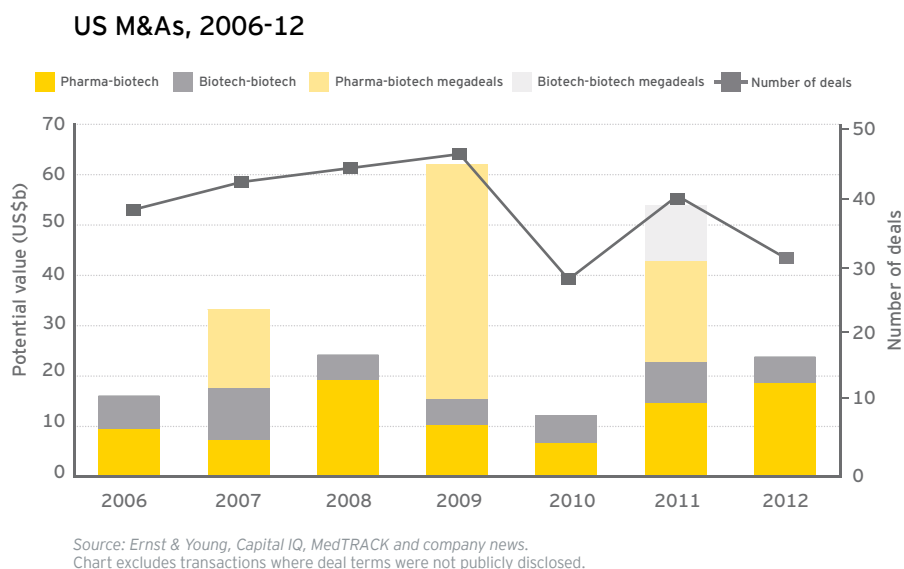
Firepower has decreased for big pharma but increased for specialty pharma and big biotech



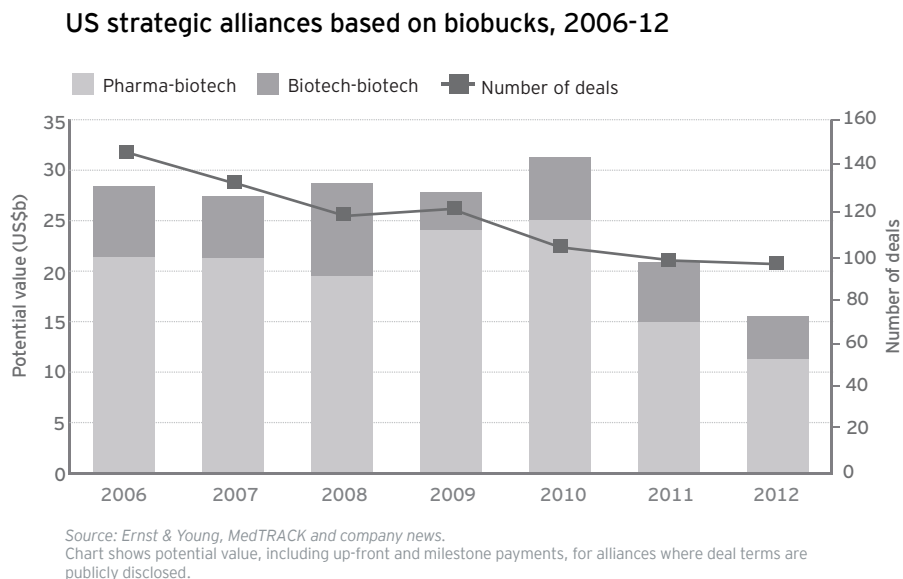
Source: Ernst & Young based on company financial report data as reported in Capital IQ. Data labels show percent change in firepower relative to 2006.

United States

M&A transactions involving US biotech companies increased by 5% to US\$23.8 billion (after adjusting for the Sanofi/Genzyme and Gilead/Pharmasset megadeals in 2011). However, both the number of transactions and the median deal size declined (the median M&A was US\$206 million in 2012, down from US\$305 million a year earlier).

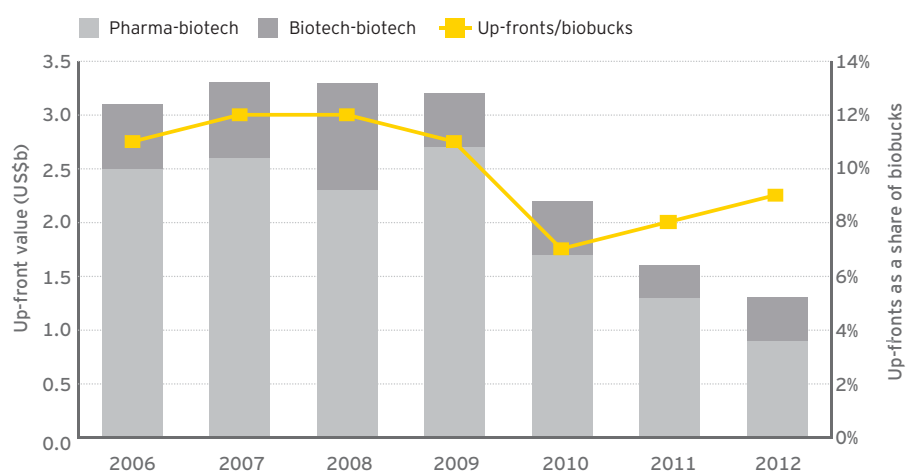


The biobucks value of strategic alliances declined for a second consecutive year, falling 26% to US\$15.5 billion. While the number of alliances was essentially flat relative to 2011 (falling from 96 to 95), the number of transactions has been on a long-term downward trajectory since 2006.



The story was no better when looking at up-front payments, which fell to US\$1.3 billion, a 19% decline from 2011. Up-front payments are down 61% from their 2008 peak. While up-front payments as a share of biobucks ticked up to 9%, they are still well below the levels seen between 2006 and 2009.

US strategic alliances based on up-front payments, 2006-12



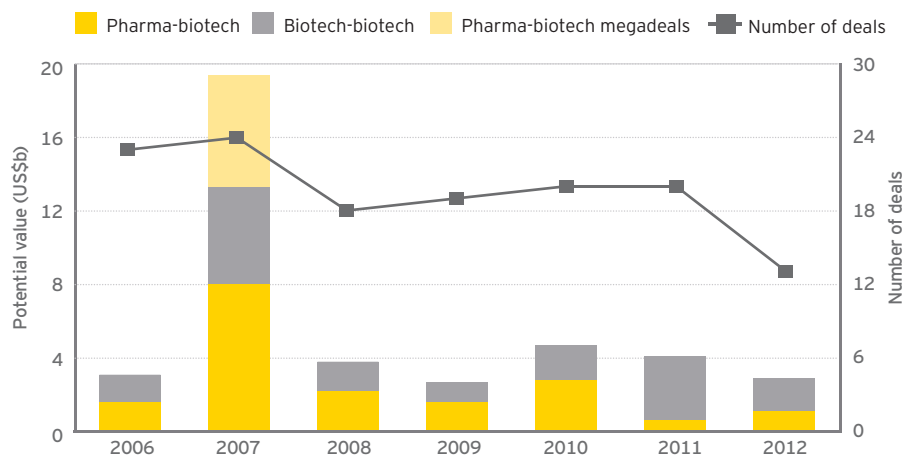
Source: Ernst & Young, MedTRACK and company news.



Europe

While M&A activity rose in the US (on a megadeal-adjusted basis), in Europe both the volume and value of transactions was down. The value of M&As declined 28% to US\$2.9 billion, and the number of deals with announced terms fell to 13 – the lowest level since at least 2005. Pharma played a larger role than in the prior year, correcting the disproportionately large share of biotech-biotech deals in 2011 and mirroring a similar shift in the US.

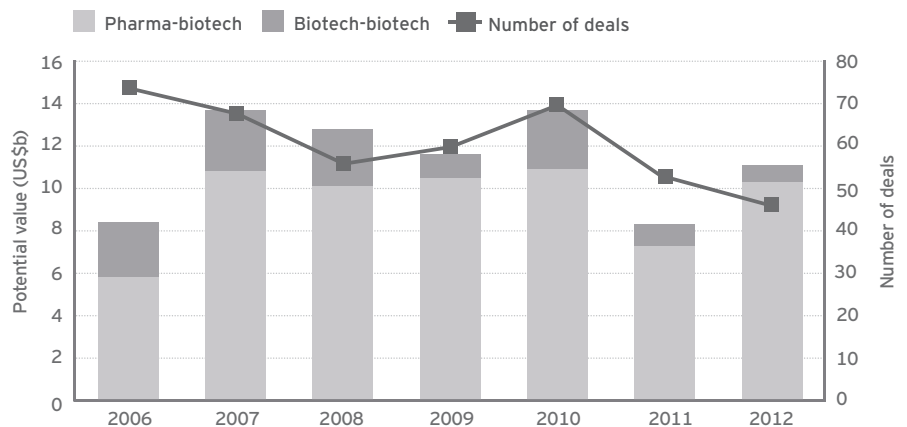
European M&As, 2006-12



Source: Ernst & Young, Capital IQ, MedTRACK and company news.
Chart excludes transactions where deal terms were not publicly disclosed.

In Europe, total biobucks value of strategic alliances rebounded in 2012, increasing by 34% to US\$11.1 billion. However, the number of alliances fell to a seven-year low, to 46. These shifts were in direct contrast to the trend in the US, where the biobucks value of alliances fell while the number of deals held steady. Pharma's domination of the strategic alliance scene grew, as the proportion of biotech-biotech deals fell even further. Platform companies were highly visible among Europe's deal makers.

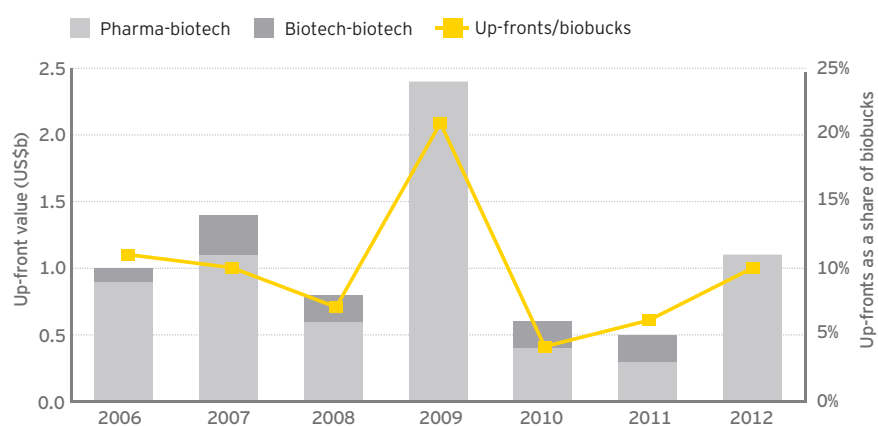
European strategic alliances based on biobucks, 2006-12



Source: Ernst & Young, MedTRACK and company news.
Chart shows potential value, including up-front and milestone payments for alliances where deal terms are publicly disclosed.

Up-front payments increased by a very solid 135% to US\$1.1 billion – an encouraging development given that these payments, rather than biobucks, represent the cash that companies actually receive when a deal is signed. However, the biobucks total is still well below the levels seen between 2006 and 2009. The dominance of big pharma buyers was even more apparent in up-front payments than in biobucks, and biotech-biotech deals accounted for only 3% of total up-front payments in 2012.

European strategic alliances based on up-front payments, 2006-12



Source: Ernst & Young, MedTRACK and company news.





Products and pipeline

A banner year

The big picture

The analysis in other sections of this report (e.g., the *Financing* article) often contrasts the years before and after the start of the global financial crisis. When it comes to product approvals and pipeline development, however, the financial crisis had little or no discernible impact. Instead, product approvals had slowed down well before the crisis. In the US, for instance, the number of FDA approvals has been markedly slower since 2005, when safety concerns came to the forefront and increasing pressure from policy makers caused the FDA to take an exceedingly cautious approach to product approvals.

In 2011, the number of FDA product approvals increased significantly for the first time in seven years. Like many others, we were encouraged by this development but unsure whether it represented a one-year blip or a more sustained shift. In 2012, the answer was apparent when the number of FDA approvals increased sharply, to levels not seen since 1997. To put that in context, the last time the FDA approved this many products, the president of the

United States was Bill Clinton and the human genome had not yet been sequenced. Similar strength was apparent in Europe, where a number of significant products were approved by regulators.

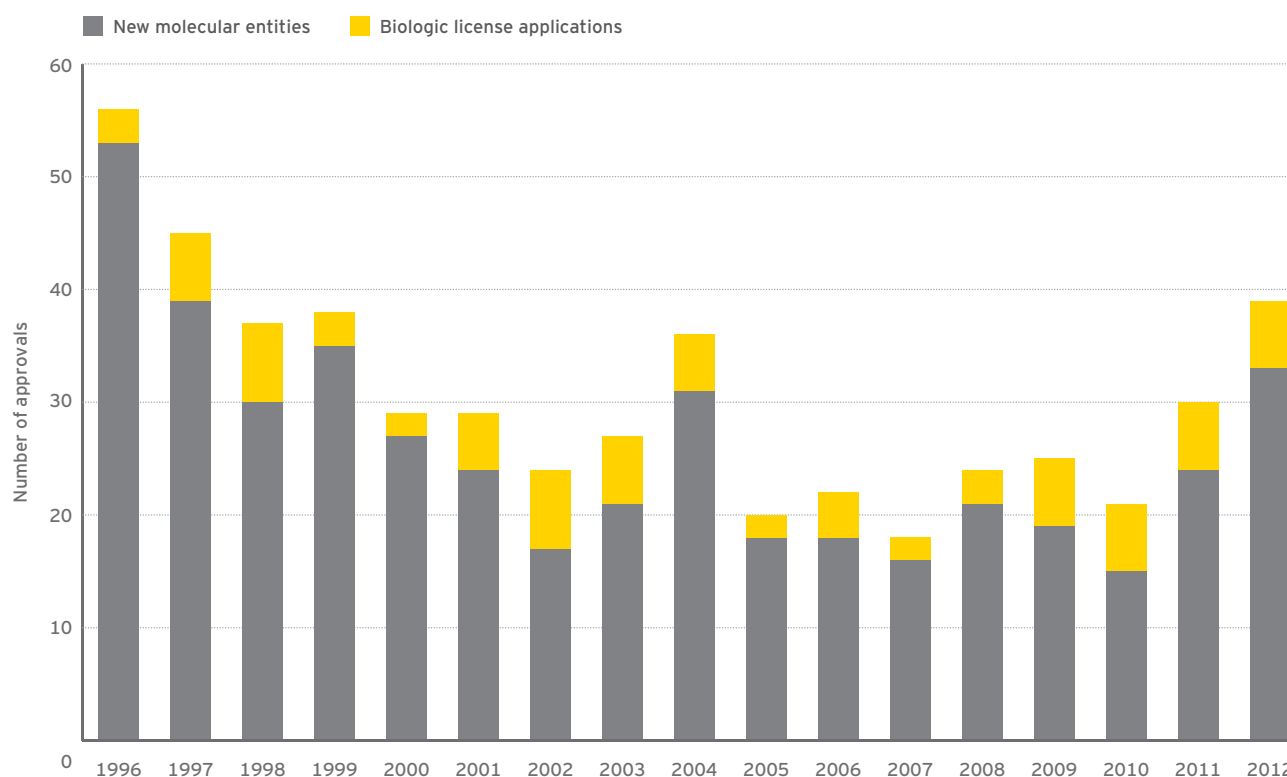
We are encouraged not just by the number of approvals, but by the nature of products being approved. Many of the year's approvals were not me-too offerings but first-in-class treatments that seek to address genuine unmet needs. Significant numbers of new products are for orphan indications and/or based on personalized medicine approaches.

This is encouraging news for investors concerned about regulatory risk and the time and expense associated with developing new products. It is potentially good news for pharma companies seeking to replenish their pipelines. Ultimately, of course, it is positive news for the many patients who need breakthrough treatments for increasingly urgent health challenges.



United States

FDA product approvals, 1996-2012



Source: Ernst & Young, FDA.
US product approvals are based on CDER approvals only.

The number of product approvals – new molecular entities (NMEs) and biologic license applications (BLAs) – by the U.S. Food and Drug Administration (FDA) soared for the second consecutive year. In 2012, the FDA approved 39 products: 33 NMEs and 6 BLAs. This was the highest number of FDA approvals since 1997.

Perhaps as a reaction to the criticism that the FDA has received from industry and patient groups seeking access to medicines, the agency is highlighting not just the large number of approvals but also the speed with which they were approved (all but one drug met target dates for application review and 79% of them met target dates for application review) and the fact that many

of the products were innovative medicines that addressed genuine unmet needs (51% were first-in-class medications and 33% were orphan drugs).

Twelve of the products approved were in oncology, while gastrointestinal and respiratory indications saw four approvals each.

Pfizer secured four product approvals and a fifth (Eliquis) that it will co-market with BMS. The uptick in approvals is encouraging news for big pharma companies, which are looking for new products to fill the gap left by recent expiration of some of their biggest blockbuster products.

Selected orphan drug approvals by the FDA, 2012

Company	Brand name	Generic name	Type of approval	Indication	Review classification	Month
Vertex Pharmaceuticals	Kalydeco	Ivacaftor	New molecular entity	Cystic fibrosis	Priority	January
BTG International	Voraxaze	Glucarpidase	New biologic license application	Toxic levels of methotrexate due to kidney failure	Priority	January
Pfizer	Elelyso	Taliglucerase alfa	New molecular entity	Gaucher's disease	Standard	May
Onyx Pharmaceuticals	Kyprolis	Carfilzomib	New molecular entity	Multiple myeloma	Standard	July
Pfizer	Bosulif	Bosutinib monohydrate	New molecular entity	Chronic myelogenous leukemia	Standard	September
Ivax International	Synribo	Omacetaxine mepesuccinate	New molecular entity	Chronic myelogenous leukemia	Standard	October
Exelixis	Cometriq	Cabozantinib	New molecular entity	Medullary thyroid cancer	Priority	November
NPS Pharmaceuticals	Gattex	Teduglutide recombinant	New molecular entity	Short bowel syndrome	Standard	December
Ariad Pharmaceuticals	Iclusig	Ponatinib hydrochloride	New molecular entity	Chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia	Priority	December
Aegerion	Juxtapid	Lomitapide	New molecular entity	Homozygous familial hypercholesterolemia	Standard	December
Human Genome Sciences	ABthrax	Raxibacumab	New biologic license application	Inhalational anthrax	Priority	December
Novartis	Signifor	Pasereotide diaspertate	New molecular entity	Cushing's disease	Standard	December
Johnson & Johnson	Sirturo	Bedaquiline fumarate	New molecular entity	Multi-drug-resistant pulmonary tuberculosis	Priority	December

Source: Ernst & Young, FDA and company websites.

Out of the 39 products approved by the FDA in 2012, 13 were orphan drugs. This partly reflects the fact that orphan indications have become a focus area for drug development companies. Companies are attracted not just by the economic incentives for orphan drug development, but also by the perception that increasingly demanding payers are more likely to reimburse products that serve genuine unmet medical needs. (For more on these considerations, refer to this year's *Point of view* article.)

Noteworthy orphan drug approvals include Vertex Pharmaceuticals' Kalydeco (for a rare form of cystic fibrosis caused by a specific genetic mutation), Ariad Pharmaceuticals' Iclusig (for two rare forms of leukemia) and Onyx Pharmaceuticals' Kyprolis (for multiple myeloma).

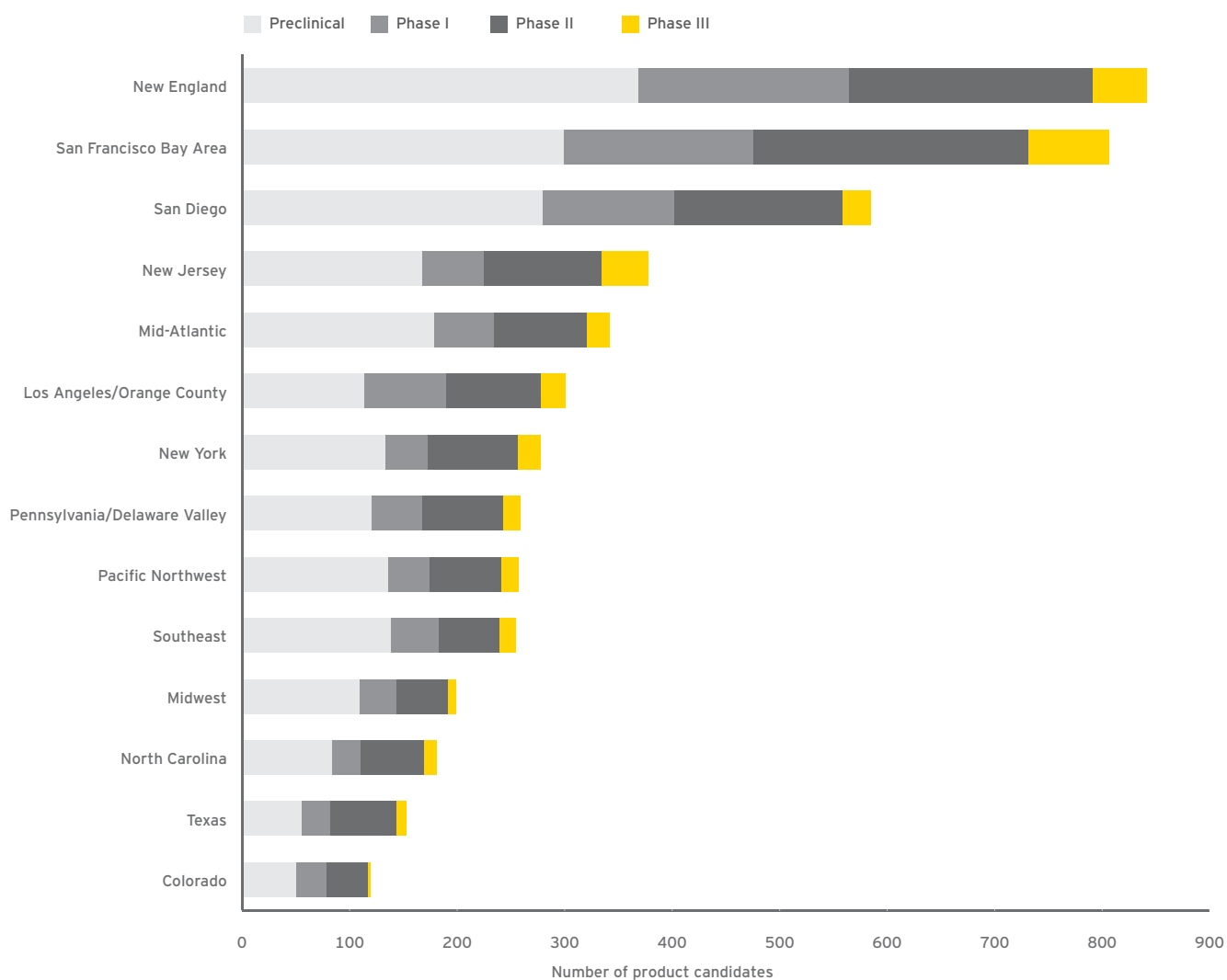
Other selected FDA approvals, 2012

Company	Brand name	Generic name	Type of approval	Indication	Month
Roche (Genentech)	Erivedge	Vismodegib	New molecular entity	Basal cell carcinoma	January
Eli Lilly	Amyvid	Florbetapir F 18 injection	New molecular entity	Radioactive diagnostic agent for Alzheimer's disease	April
Roche (Genentech)	Perjeta	Pertuzumab	New biologic license application	HER2-positive metastatic breast cancer	June
Teva	Neutroval	Tbo-filgrastim	New biologic license application	Neutropenia and neutrophils	August
Gilead Sciences	Stribild	Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	New molecular entity	HIV-1 infection	August
Astellas	Xtandi	Enzalutamide	New molecular entity	Metastatic castration-resistant prostate cancer	August
Sanofi	Zaltrap	Ziv-aflibercept	New biologic license application	Colorectal cancer	August
Bayer	Stivarga	Regorafenib	New molecular entity	Metastatic colorectal cancer	September
ThromboGenics	Jetrea	Ocriplasmin	New biologic license application	Symptomatic vitreomacular adhesion	October
Bristol-Myers Squibb	Eliquis	Apixaban	New molecular entity	Stroke and systemic embolism	December
Salix Pharmaceuticals	Fulyzaq	Crofelemer	New molecular entity	HIV-associated diarrhea	December

Source: Ernst & Young, FDA and company websites.

Noteworthy non-orphan product approvals during the year include some first-in-class drugs, such as Amyvid (the first brain scan imaging agent to help rule out Alzheimer's disease), Erivedge (the first FDA-approved drug for late-stage basal cancer) and Fulyzaq (the first drug approved for HIV-associated diarrhea).

US pipeline by region

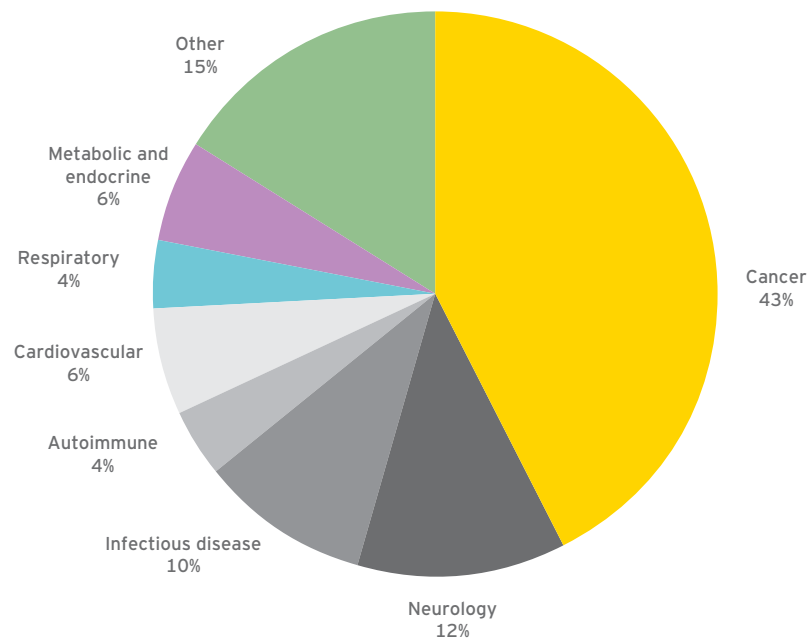


Source: Ernst & Young, MedTRACK and company websites.

As might be expected, the geographic distribution of the US biotechnology industry's pipeline is strongly correlated with the size of local clusters. New England, the San Francisco Bay Area and San Diego take the top three spots. New England, which has more start-ups than any other cluster, has the largest early-stage (preclinical and Phase I) pipeline, while the San Francisco Bay Area, which has relatively more mature companies, has the largest Phase II and Phase III pipelines.

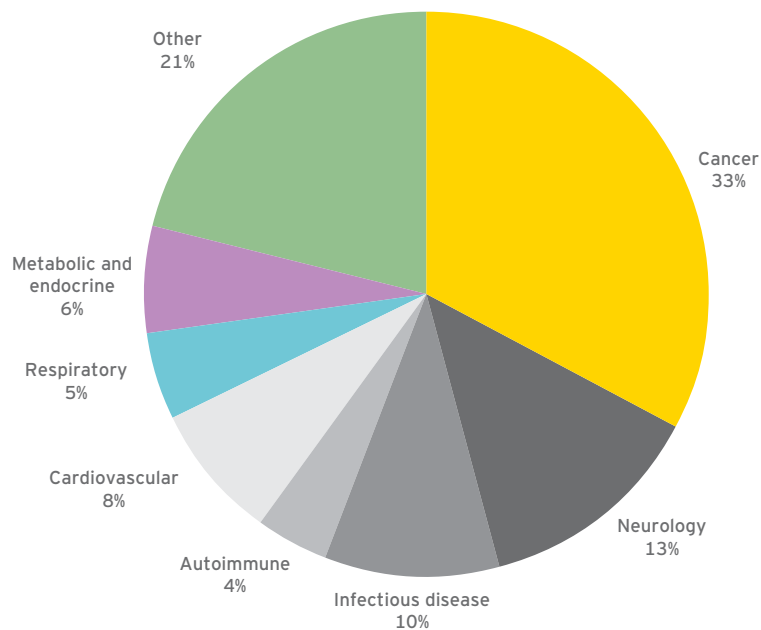
Cancer remains the biggest focus, accounting for 43% of the US biotech industry's pipeline and a third of the Phase III pipeline. Infectious diseases, which account for 10% of the pipeline, are particularly important in an era of increasingly resistant pathogens, though the economics has sometimes been challenging. Chronic diseases, in categories such as cardiovascular and metabolic and endocrine, are projected to be a large market thanks to aging populations and sedentary lifestyles.

US clinical pipeline by indication, 2012



Source: Ernst & Young, MedTRACK and company websites.

US Phase III pipeline by indication, 2012



Source: Ernst & Young, MedTRACK and company websites.

Europe

Selected orphan drug approvals by the EMA, 2012

Company	Brand name	Generic name	Indication	Month
Nova Laboratories	Xaluprine	6-mercaptopurine monohydrate	Acute lymphoblastic leukemia	March
Pharmaxis	Bronchitol	Mannitol	Cystic fibrosis	April
Novartis	Signifor	Pasereotide diaspertate	Cushing's disease	April
Vertex Pharmaceuticals	Kalydeco	Ivacaftor	Cystic fibrosis	July
Novartis	Jakavi	Ruxolitinib	Disease-related splenomegaly or symptoms of primary myelofibrosis, post-polycythaemia-vera myelofibrosis or post-essential-thrombocythaemia	August
Takeda (Nycomed)	Revestive	Teduglutide	Short-bowel syndrome	August
Johnson & Johnson (Janssen-Cilag)	Dacogen	Decitabine	Acute myeloid leukemia	September
Takeda (Millenium)	Adcetris	Brentuximab vedotin	Hodgkin lymphoma	October
uniQure	Glybera	Alipogene tiparvovec	Familial lipoprotein lipase deficiency	October
Teva (Ivax)	NexoBrid	Concentrate of proteolytic enzymes enriched in bromelain	Thermal burns	December

Source: Ernst & Young, EMA and company websites.

As in the US, Europe saw a number of orphan drug approvals in 2012. Glybera became the first gene therapy drug approved in the Western world when Netherlands-based uniQure secured approval for the product in October. Gene therapy, an area that was considered very promising in biotech's early years, was bedeviled for years with R&D setbacks and safety concerns. The approval of Glybera, a therapy for a rare disease which leaves people unable to properly digest fats, is therefore a notable achievement.

There were two products approved for cystic fibrosis: Vertex Pharmaceuticals' Kalydeco (which was approved a few months earlier by the FDA in the US) and Bronchitol, developed by Australia's Pharmaxis (which had been approved by Australian regulators in 2011).

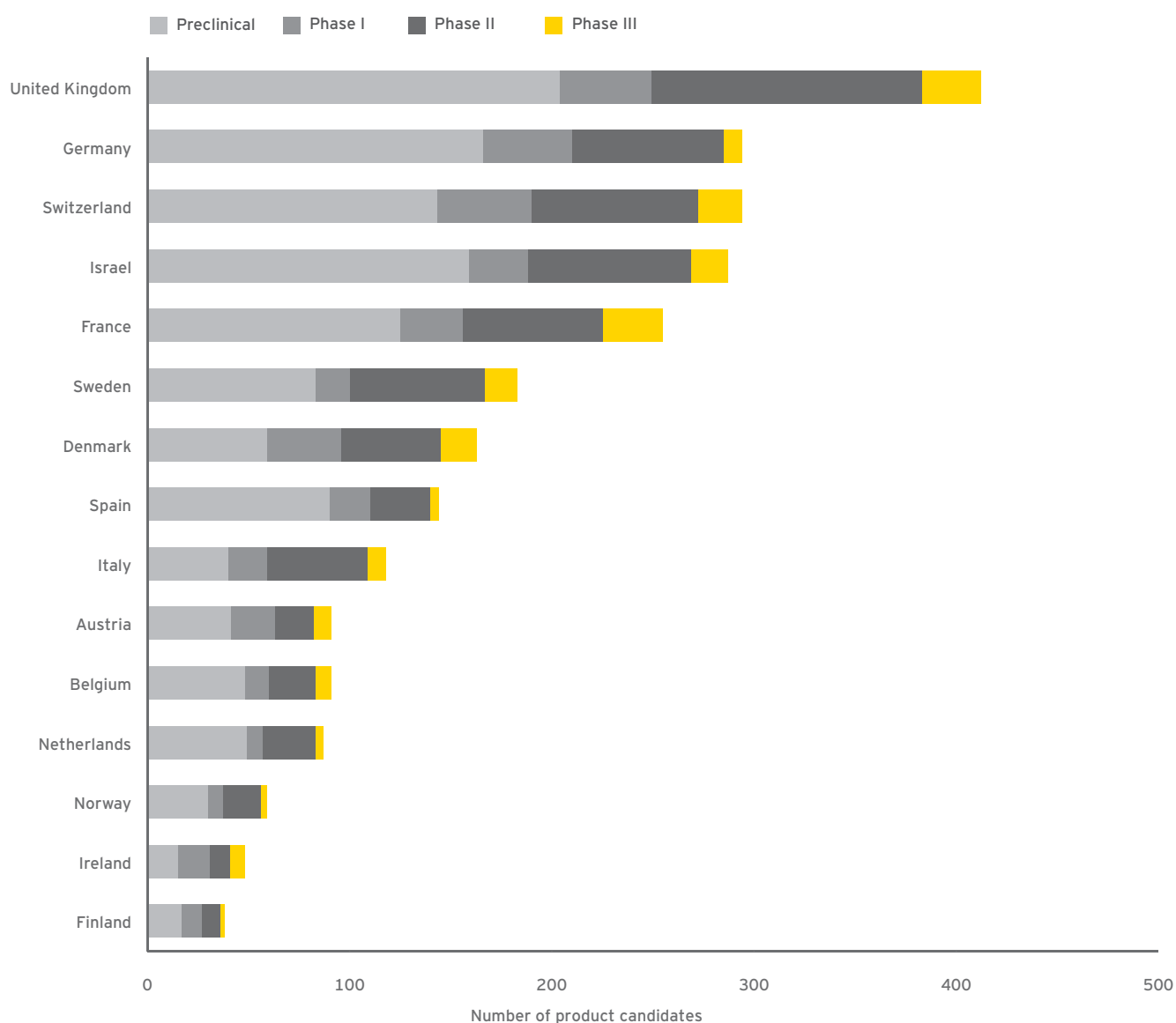
Other selected EMA approvals by European companies, 2012

Company	Country	Brand name	Generic name	Month	Indication
AstraZeneca	UK	Caprelsa	Vandetanib	February	Medullary thyroid cancer
Roche	Switzerland	Zelboraf	Vemurafenib	February	BRAF-V600-mutation-positive unresectable or metastatic melanoma
GlaxoSmithKline	UK	Nimenrix	Meningococcal group A, C, W-135 and Y conjugate vaccine	April	Meningitis
Sanofi	France	Riluzole Zentiva	Riluzole	May	Amyotrophic lateral sclerosis
Almirall	Spain	Bretaris/Eklira Genuair	Acridinium bromide, micronised	July	Chronic obstructive pulmonary disease
Boehringer Ingelheim	Germany	Jentaduet	Linagliptin/metformin	July	Type 2 diabetes mellitus
AstraZeneca	UK	Zinforo	Ceftaroline fosamil	August	Complicated skin and soft tissue infections and community-acquired pneumonia
Novartis	Switzerland	Enurev Breezhaler	Glycopyrronium bromide	September	Chronic obstructive pulmonary disease
Novo Nordisk	Denmark	NovoThirteen	Catridecacog	September	Congenital factor-XIII-A-subunit deficiency
Novartis	Switzerland	Seebri/Tovanor Breezhaler	Glycopyrronium bromide	September	Chronic obstructive pulmonary disease
Almirall	Spain	Constella	Linacotide	November	Irritable bowel syndrome
Bayer	Germany	Eylea	Aflibercept	November	Neovascular age-related macular degeneration
AstraZeneca/Bristol-Myers Squibb	UK	Forxiga	Dapagliflozin propanediol monohydrate	November	Type 2 diabetes mellitus
Merz Pharmaceuticals	Germany	Memantine Merz	Memantine hydrochloride	November	Alzheimer's disease

Source: Ernst & Young, EMA and company websites.

Not surprisingly, noteworthy 2012 product approvals in Europe included some first-in-class cancer drugs. Caprelsa is the first treatment approved in Europe for aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Zelboraf is the first and only personalized skin cancer medicine for patients with BRAF V600 mutation-positive metastatic melanoma. There were also several approvals targeting chronic diseases (chronic obstructive pulmonary disease, Type 2 diabetes, Alzheimer's disease).

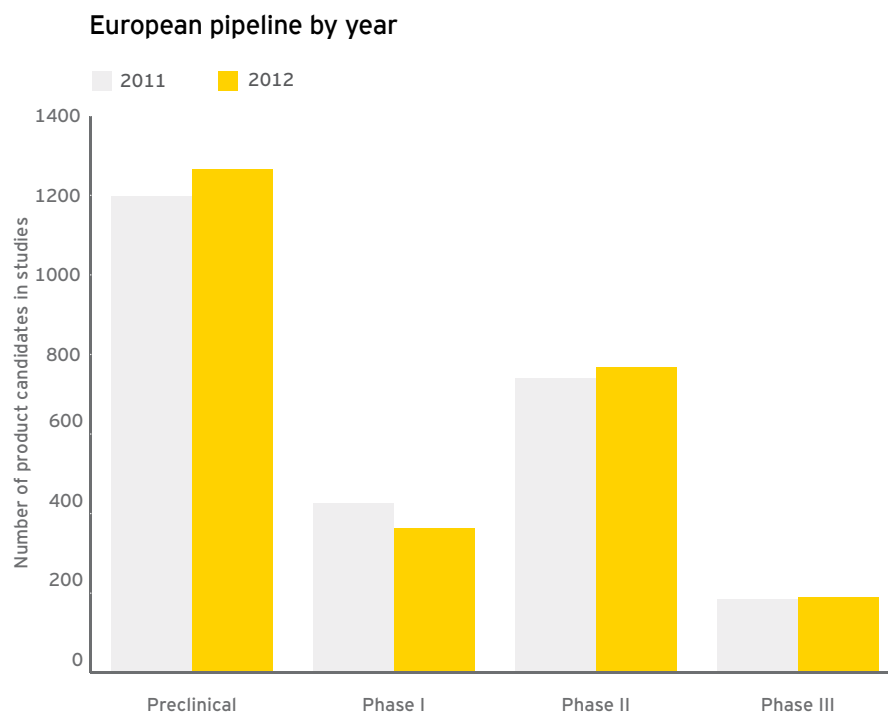
European pipeline by country



Source: Ernst & Young, MedTRACK and company websites.

Europe's pipeline is about half the size of the US pipeline. In 2012, the UK, Germany and Switzerland accounted for nearly 40% of the European total. The UK has the largest number of drug candidates in preclinical studies and Phase II trials, while France has a small lead in the number of Phase III trials.

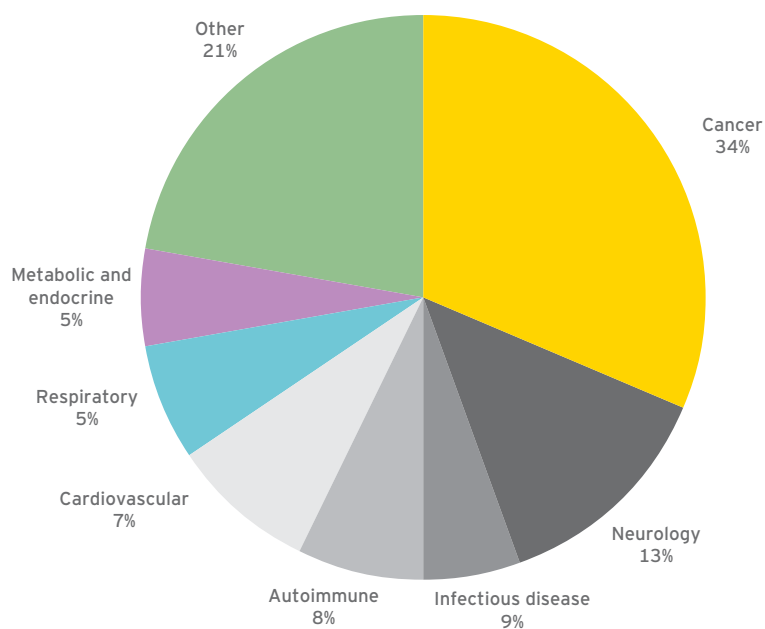
The aggregate pipeline of European biotechnology companies grew by 1.5% relative to 2011. While the number of candidates in Phase I trials declined, there were increases in the number of items in preclinical studies as well as Phase I and Phase II trials.



Source: Ernst & Young, MedTRACK and company websites.



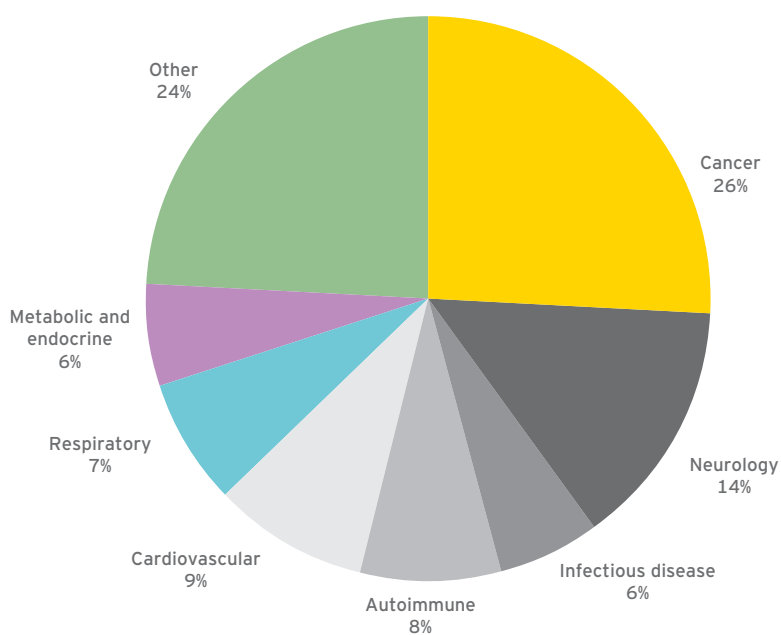
European pipeline by indication



As in the US, oncology was the top indication in terms of pipeline focus.

Source: Ernst & Young, MedTRACK and company websites.

European Phase III pipeline by indication, 2012



Source: Ernst & Young, MedTRACK and company websites.



Acknowledgments

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Glen Giovannetti, Ernst & Young's Global Life Sciences Leader, provided overall strategic vision for this report and brought his years of experience to the analysis of industry trends. He also brought a hands-on approach, writing articles and helping to compile and analyze data.

Gautam Jaggi, Managing Editor of the publication, directed the project, wrote or edited all of the articles and helped manage the data analysis. Gautam developed several of the themes and elements for this year's report, including writing the *Point of view* article, and had responsibility for the entire content and the quality of the publication.

Siegfried Bialojan, Germany Biotechnology Leader, and **Jürg Zürcher**, EMEA Biotechnology Leader, led and managed the development of the European content. Siegfried's team conducted the data analysis used in this report.

Jason Hillenbach, who served as Project Manager, was responsible for keeping the project running smoothly. Among other things, Jason allocated resources, managed quality review of the data, developed insights for the articles and managed numerous logistical issues.

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