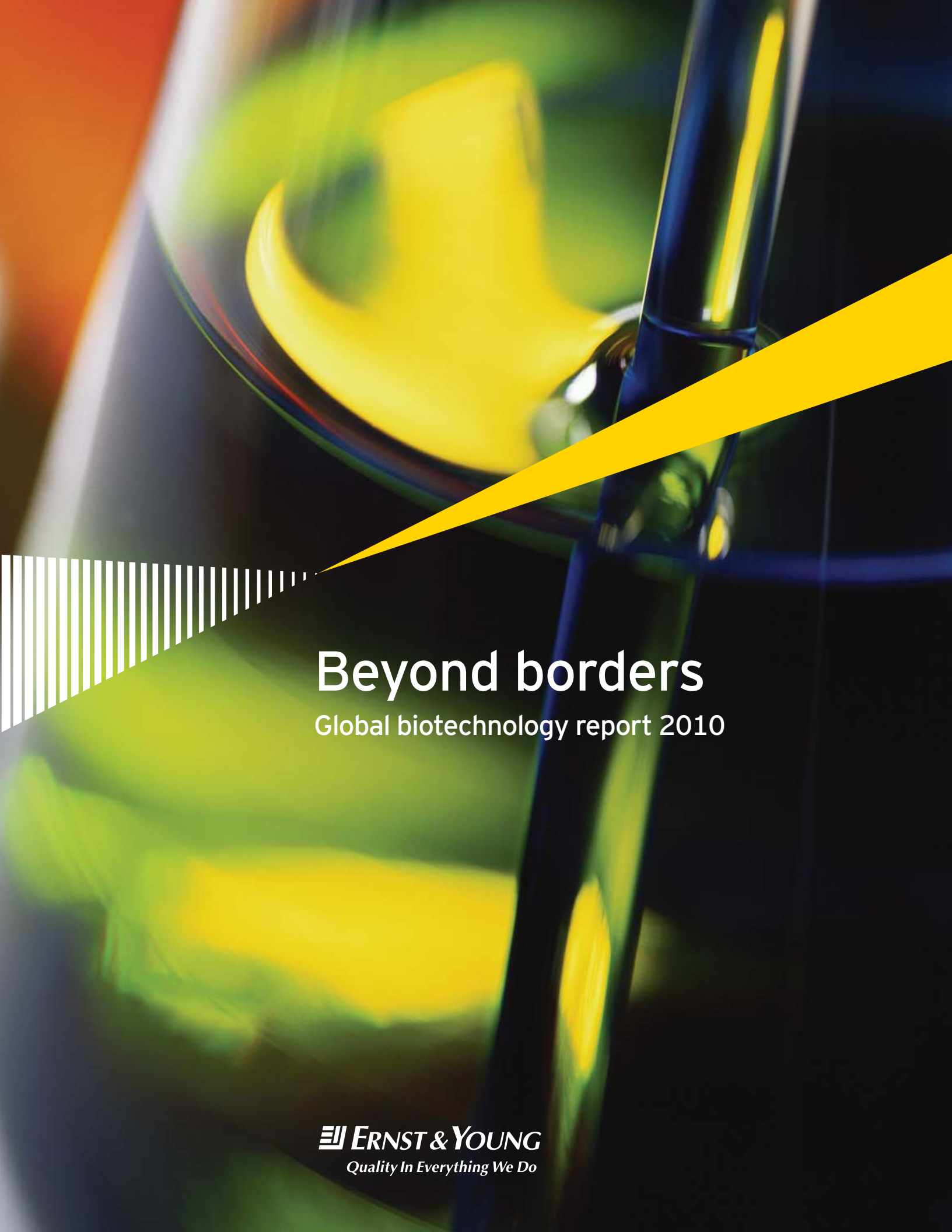

Beyond borders

Global biotechnology report 2010

Ernst & Young

Quality In Everything We Do

To our clients and friends

As economies around the world begin to recover from the worst economic crisis since the Great Depression, it is clear that a "new normal" is emerging. Among other things, this is a world in which capital flows are far more constrained than during the easy money-fueled decade that preceded the downturn. What impact has this capital-constrained environment had on biotechnology — a business that is based on an enormous hunger for capital coupled with an exceptionally long path to commercial payback?

We set out to answer that question in this year's *Beyond borders*. As usual, we analyze key indicators of the industry's performance: financing activity, deal trends, financial results, pipeline strength and product approvals. While the overall results are robust, the gap between the industry's haves and its have-nots has widened.

Our *Global introduction* article pulls together these trends and assesses their implications for biotechnology companies. In particular, we focus on new models and creative approaches that companies and investors are taking to adapt to today's challenging economic climate. Accompanying our article are six *Perspectives for the new normal* by leaders of companies that are using innovative approaches to finance companies, raise capital, conduct R&D and structure deals.

The common thread that runs through this discussion — indeed, the mantra of the new normal — is the search for efficiency. In a time of diminished means, key constituents in the biotechnology ecosystem — investors, pharmaceutical companies, payors, governments and biotech firms — need to do more with less. Companies that are able to develop creative solutions to boost efficiency will be best positioned to succeed in the new normal.

Readers of *Beyond borders* will notice some structural changes in this year's report. In prior years, we organized the report by geography, with sections on the Americas, Europe and Asia-Pacific. This year, we have instead organized the report thematically. The *Global perspective* section brings together our point of view on salient trends and implications as well as some perspectives from company leaders. This is followed by a *Country profiles* section, where we summarize key developments in countries with developing biotechnology sectors. In the *Industry performance* section, we analyze data from locations with established biotechnology centers: the US, Europe, Canada and Australia. We think this allows us to more appropriately analyze developments in markets of different maturity and allows readers to more easily access and compare thematic trends.

Ernst & Young's life sciences professionals stand ready to help you as you navigate the unprecedented challenges and opportunities in the new normal.

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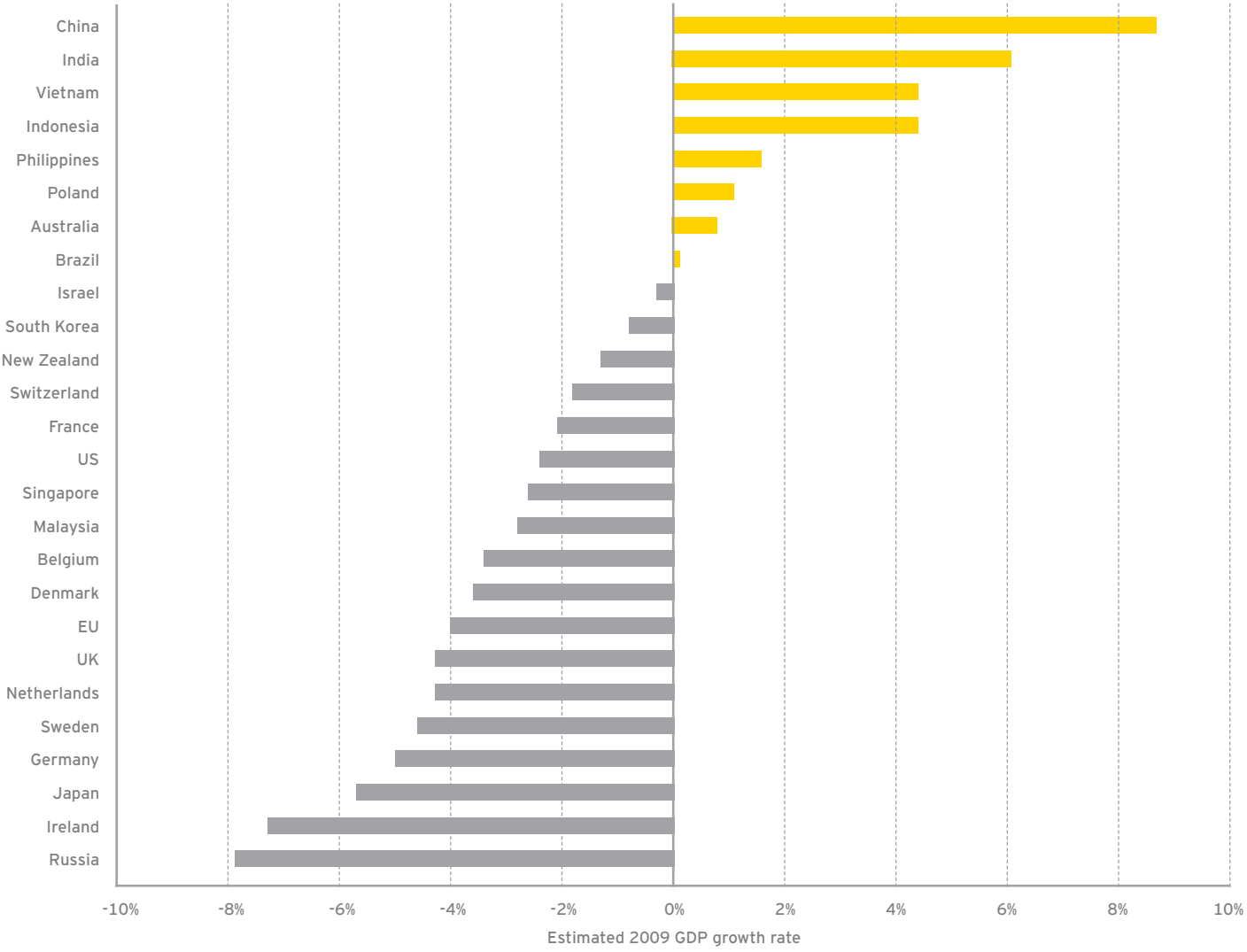
The new normal

Last year's *Beyond borders* was written in late 2008 and early 2009, in the darkest depths of the global financial crisis. In those dramatic months – as policy-makers and regulators struggled to avert a total meltdown of global banking and finance – stock markets plummeted, credit froze and capital seized up. Amid pervasive uncertainty, many emerging biotechnology companies took drastic restructuring measures, focusing pipeline development efforts, trimming payrolls and even selling assets.

Not surprisingly, last year's *Global introduction* article ("Beyond business as usual?") dwelt on these developments and their likely impact on the biotech business model. Despite restructuring efforts, we predicted that there would be a significant reduction in the number of companies, and that access to capital would likely remain constrained for the foreseeable future. We worried about the implications

The not-quite-global crisis: estimated GDP growth rates in 2009



Source: CIA World Factbook

for biotech's sustainability – that the business model the industry has long thrived on would be starved of its key input (funding) and companies' efforts to cull their pipelines would lower the model's key output (innovation). We wondered whether recovery, when it came, might bring not a return to normal, but rather the emergence of a "new normal," requiring new models for sustainability. And we described four paradigm-shifting trends that could potentially create a path to more sustainable business models in the future.

A year later, the dust has settled and the outlines of a new normal are indeed starting to emerge. In both the general economy and the biotech industry, the worst is clearly over, but things are not reverting to business as usual. And in many ways, the experience of the global biotech industry so far has mirrored that of the global economy.

For one, while the downturn is commonly referred to as the global financial crisis or global recession, it has, in reality, had divergent impacts on different parts of the globe. While most industrialized nations and many developing countries suffered through recessions in 2009, some emerging economies – most notably China and India – continued to see unabated economic growth.

While several economies have started to emerge from recession in late 2009 and early 2010 (based on the official yardstick of GDP growth) and global stock markets are approaching pre-crisis levels, unemployment has remained stubbornly high, particularly in the US. The worst of the credit crisis has successfully been abated, but bank lending standards remain tight. This, coupled with an uncertain market environment, has lowered hiring at small businesses – traditionally a key engine of job creation. Amid talk of a prolonged "jobless recovery," most economists now expect that high unemployment levels will remain part of the new normal for some time to come, with potential implications for economic and social stability.

The situation for biotech is similarly mixed. On the surface, it would appear that the worst is indeed over. Aggregate funding levels rebounded nicely in 2009 and strategic alliance activity remains robust. Financial performance has been fairly strong – particularly under the circumstances – with remarkable improvement on the bottom line as companies have engaged in belt tightening. The market cap of smaller companies, which had taken a beating, has rebounded impressively, making up much of the ground that was ceded in late 2008 and early 2009. (For more on these trends, refer to the *Industry performance* section.)

Haves and have-nots: more of the same?

While the overall numbers mentioned above – capital raised, alliance activity, profitability – are heartening, they only tell part of the story. Economic dislocations produce winners and losers, and the real impact is found not in aggregates and averages but in measures of variance and standard deviation. While aggregate financing levels have held up well, the availability of capital is challenging for many companies.

Indeed, our analysis shows that the distribution of funding has become more skewed during the last year. In the US, for instance, the top 20% of fund-raising companies garnered 74.1% of capital raised in 2008. In 2009, the proportion raised by the same quintile of companies had increased, to 78.5%. Conversely, the 20% of companies that raised the least funding got only 0.9% of capital in 2008 and saw their share shrink even further to a paltry 0.6% in 2009.

Haves and have-nots: the distribution of financing has become increasingly skewed

Quintiles of companies based on capital raised in 2009	Share of US capital raised in:				
	2005	2006	2007	2008	2009
Quintile 1	68.7%	74.1%	70.6%	74.1%	78.5%
Quintile 2	16.3%	13.4%	15.6%	14.2%	12.5%
Quintile 3	10.3%	7.4%	8.6%	7.5%	5.9%
Quintile 4	3.7%	4.0%	3.9%	3.3%	2.4%
Quintile 5	1.0%	1.1%	1.3%	0.9%	0.6%

Source: Ernst & Young

Of course, this is not a novel development. Biotech has long been an industry of haves and have-nots, and many of the trends we are seeing in the current market – a challenging IPO environment, investors looking for de-risked investments – have been apparent well before the onset of the financial crisis. While the distribution of financing certainly became more unequal in 2009, this in fact only continues a steady skewing that has been under way for several years.

Still standing: resilience by any other name

In the 24 years that we have been producing annual reports on the biotechnology industry, we've seen some recurring themes. Principal among these, perhaps, is the industry's remarkable ability to endure through challenging times. Indeed, the titles of many of our reports – *Endurance, Refocus, Resurgence, Resilience*, to name a few – testify to the creativity and nimbleness that biotech companies have shown in crises past.

Despite that storied track record, we expected this downturn and recovery to be different. Unlike previous funding droughts, the current crisis has not been driven by vacillating investor sentiment toward biotech stocks, but rather by a fundamental and systemic recalibration of credit and capital markets. Anticipating a sustained reduction in the availability of capital and a relatively slow recovery, we expected a sharp reduction in the number of firms in 2009.

So far, that has largely not happened. Call it what you will – resilience, flexibility, durability – this industry has it in spades. As of December 2008, an extremely large share of public companies – 37% of European companies, 44% of US entities and an incredible 57% of Canadian firms – had less than a year of cash on hand. With investors being more selective, we expected that many of these firms would not survive the year as independent going concerns. As it turns out, though, most of those companies did survive, and the number of public biotech companies in established centers shrunk by only 11%, much less than the 25%–33% reduction many analysts and industry observers were expecting.

What happened? To get a better sense of the story, we went back and looked at the cohort of US companies that had less than a year of cash as of December 2008 to see how they fared during the following year. As one would expect, some of those firms – 13% of the total, in fact – were no longer around a year later, either because they ceased operations or because they were acquired. Another 57% of companies were hanging on but still had less than a year of cash on hand, and we certainly expect to see continued attrition in this group in 2010 – a continuation of the Darwinian process we described in last year's report.

> "Efficiency has become, in many ways, the mantra of today's economic times. In an era of diminished means, the need to do more with less … is being felt by consumers, corporations and countries."

The remaining 30% of companies, however, were able to move up the survival index, and 9% had even moved all the way to the top cohort, with more than five years of cash on hand.

Some companies were able to do this by raising capital despite the challenging environment. In fact, 21% of capital raised by US public companies during 2009 went to firms that had less than one year of cash as of December 2008, while another 25% went to firms that had 1–2 years of cash on hand. Those are impressive totals, but there was a haves-and-have-nots story here, too. More than 40% of the money raised in these two cohorts went to just four companies, two of which – Human Genome Sciences and Dendreon – were able to raise exceptionally large sums on the back of positive clinical trial news.

Clearly, a key driver of survival for many companies was their ability to find ways of operating more efficiently. This is not entirely surprising, since efficiency has become, in many ways, the mantra of today's economic times. In an era of diminished means, the need to do more with less (i.e., boost efficiency or output per unit of input) is being felt by consumers, corporations and countries. The big legislative issues of the day – from energy policy to health care reform – are also fundamentally about the search for more efficient solutions. (Media coverage of US health care reform has often focused on expanding access to insurance, but the legislation is really about expanding access while containing costs – and to achieve those somewhat contradictory goals will inevitably require increasingly efficient ways of delivering health care.) And by the same token, the constituents of the biotech ecosystem are being challenged as never before to find more efficient ways to deploy scarce capital, defray the high costs of R&D and share the risks and rewards of drug development.

This inevitably raises some questions that form the basis for the rest of this article. What creative approaches are companies and investors using to thrive in today's challenging times? What else might we see going forward? While each company will need to tailor its response to its individual circumstances, our analysis identifies several interesting models or approaches that are already emerging. Meanwhile, six corporate leaders highlight the relevance of their approaches in a series of pieces that accompany this article, *Perspectives for the new normal*.

To understand how innovative models may be useful in today's economic climate, we first need to understand how market realities have changed for four key stakeholders in the biotech ecosystem: investors, biotech companies, big pharma companies and payors/governments. Each of these segments faces a series of complex, often interwoven challenges — including some that predate the economic downturn.

Investors

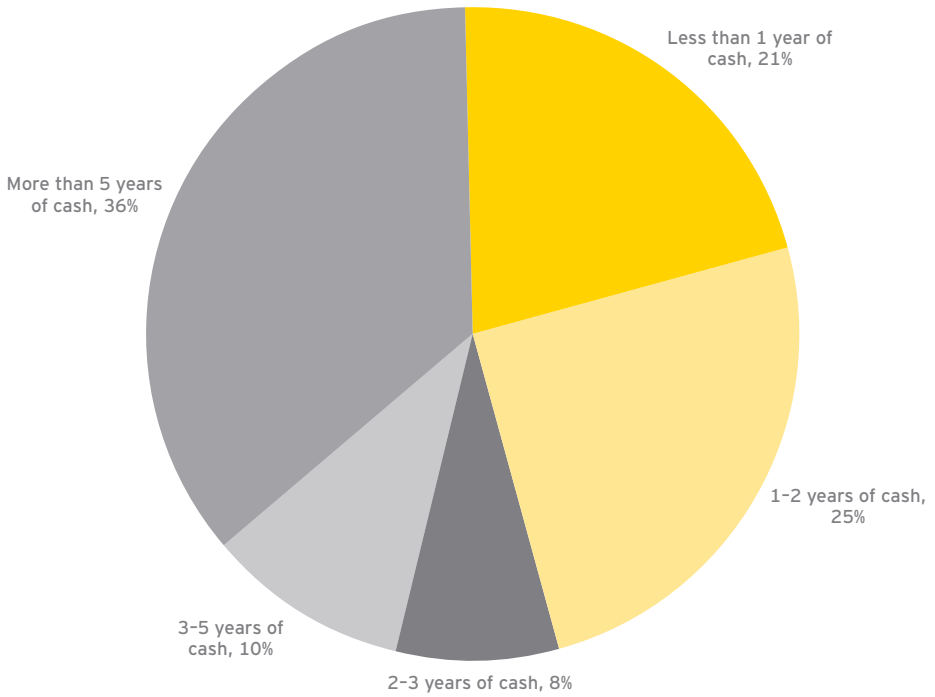
In the biotechnology industry, venture capitalists have traditionally funded portfolios of companies that have the potential to grow into fully integrated, self-sustaining enterprises. Not all companies get to realize that potential, of course — many are acquired along the way — but companies and investors have typically earned the best returns by retaining at least some control over a product's commercial destiny. This funding model requires significant investments in infrastructure and workforce, and, given biotech's long product-development cycles, investors inevitably have to "pass the baton" to successive rounds of backers — what we termed the "world's longest relay race" in last year's *Beyond borders*.

Even before the global recession, this model has been under increasing pressure. As IPO transactions diminished and performance lagged, many VCs turned to trade sales as the primary means of exiting their investments. However, a "build it to sell it" strategy is always somewhat challenging because being acquired, unlike going public, is inherently out of one's control. A company can hope for it, even plan for it, but it can't count with any certainty on someone else being interested in acquiring it.

The global recession and the new normal that is now emerging have exacerbated the pressures on the venture investment model. As discussed above, companies seeking capital from venture investors or the public markets now face an even higher bar. For VCs, the current funding environment — where the supply of capital is constrained, IPOs are practically non-existent and exits are taking longer — has also increased the need to deploy capital efficiently.

What new funding models are emerging to sustain biotech innovation? How will capital be deployed in the new normal? While we do not expect to see the wholesale demise of the venture funding model that has existed for decades, the share of capital following the traditional funding model will be relatively smaller, and will likely be limited to more differentiated assets and high-value platforms. Supplementing the traditional model, though, are new focused approaches that are better suited for today's economic realities.

Resilience: a few companies with low cash reserves raised significant amounts in 2009
Capital raised in 2009 by public companies and cash on hand as of 31 December 2008



Source: Ernst & Young and company financial statement data

"Since by definition, increasing efficiency requires raising the amount of output (innovation) generated per unit of input (funding), the efficiency of capital deployment and the efficiency of drug R&D are effectively two sides of the same coin."

These approaches generally have some combination of three broad types of solutions. The first of these is **lowering drug R&D costs**. This is not surprising, given the tremendously capital-intensive nature of drug development. Any model that makes an appreciable dent in R&D costs could potentially make the venture investment model more efficient, by allowing VCs to fund innovation with smaller amounts of capital. Similarly, measures that **increase the R&D success rate** could enable a more efficient use of capital by increasing the return on investment. Lastly, there has been increasing emphasis on models that allow projects to "**fail fast**." Since drug development costs increase exponentially in later stages of development, approaches that allow researchers to identify early on the ones most likely to succeed — and pull the plug on likely failures — can significantly increase the return on investment.

It is worth noting that each of these potential fixes for the venture funding model is inextricably tied to the R&D process. This is not surprising, since the vast majority of funding that VCs provide is spent in research laboratories. The returns that investors earn are, in turn, directly tied to the innovations that come out of those labs (the key output of the model, as we pointed out in last year's *Beyond borders*). Since by definition, increasing efficiency requires raising the amount of output (innovation) generated per unit of input (funding), the efficiency of capital deployment and the efficiency of drug R&D are effectively two sides of the same coin.

One approach that some investors are adopting is asset-based funding, where more early-stage venture capital is allocated to funding bare-bones research projects rather than to building full-fledged companies. Proponents of this model argue that the traditional venture funding model, with its focus on building companies, is wasteful given the very high failure rates in the early stages of R&D. In "Asset-centric financing" on page 7, Francesco De Rubertis and Michèle Ollier of Index Ventures describe their approach to asset-based funding, which allows them to take an early asset to a go/no-go point with a smaller investment than is typical in the traditional venture funding model, thereby reducing the average cost of drug development.

Of course, models based on "virtual" drug development are not new — they have been tried in various forms since at least the 1990s. The fact that they have never come close to dethroning more traditional approaches to drug development testifies to the challenges associated with virtual models. For one, it is more difficult to incentivize and motivate virtual teams of service providers around a common goal. Employees at emerging biotechs often bring a high degree of passion to pursuing the company's vision — both because of the culture of small, entrepreneurial companies as well as incentive structures that directly tie their rewards to the company's success. While the quality and variety of service providers has improved steadily over time, it is not clear that third parties working for a fixed fee can replicate the degree of ownership and passion that biotech companies typically get from their in-house teams.

But that passion, as De Rubertis and Ollier point out, can equally be a hindrance. Management and employees at traditional biotech companies can have a greater incentive to protect the survival of the enterprise rather than make decisions purely based on R&D results. To raise the next round of financing, companies may be more inclined to design a study to demonstrate that their technology has potential or is making progress rather than expose its weakness. Instead of folding up shop after the failure of their lead R&D project, management may try to hang on by in-licensing a new R&D project, which may not always be in the best interest of investors. Instead of failing fast, biotech companies sometimes end up pursuing a lingering subsistence.

Another reality of the new normal is that pharma companies are divesting assets (discussed more fully in the "Big pharma" section below), either because they are moving out of certain disease areas (e.g., after a large merger) or because they simply don't have the resources to pursue everything in their pipelines. Driven by this trend, we expect VCs and other investors to use more project-funding approaches for developing promising assets from these pools. These Symphony Capital-like models would involve the in-licensing of products from pharma companies and could include options that allow the companies to purchase the assets back at pre-negotiated prices if they hit certain development milestones.

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Francesco De Rubertis, PhD
Index Ventures
Partner

Michèle Ollier, MD
Index Ventures
Partner

Perspectives for the new normal

Asset-centric financing

One of the biggest challenges in biotech investing is deciding whether to advance or discontinue early-stage drugs in the most cash-efficient and risk-balanced manner. Yet the traditional venture approach — building a company with a portfolio of assets to diversify risk — is quite inefficient. Companies often waste scarce resources moving forward with some assets that are relatively unlikely to succeed and building infrastructure that proves unnecessary when product candidates fail.

A different approach

Index Ventures has developed an asset-centric funding model that seeks more efficient paths to success. As Roman Fleck, Principal at Index Ventures, explains, "We still finance 'traditional' biotech companies with strong platforms that can drive a sustainable pipeline of new drugs, however most of our investments are now asset-centric. In our asset-centric investments, we fund single assets and rapidly move the most promising ones to critical value infection points for partnering with, or acquisition by, pharmaceutical companies."

Our in-house VC team is supported by a close network of entrepreneurial academic and industry contacts — "asset champions," if you will. These scouts identify and help secure interesting early-stage assets, typically from universities, biotech or big pharma firms. Assets sourced from academia are usually purchased outright, with the academic institutions given a minority stake in any entity established to develop the asset. Biotech- and pharma-derived assets are secured by a variety of means, ranging from in-licensing with call-back options to direct acquisitions.

These assets typically require US$1 million to US$3 million for early work (e.g., preclinical pharmacology) to assess potential and reach a go/no-go point. Index Ventures gives each such asset the legal structure of a company — but without the attendant overhead. An entrepreneurial management team with strong project and leadership skills then drives the asset through key early-development stages. If the project fails in early development (as 9 out of 10 do), it is abandoned, and the project managers are "recycled" into the next project in the pipeline. Assets that succeed in early development are subject to our commercial hurdles (an expected return of five times or higher). We then invest significantly larger sums to advance the assets that make the cut through initial Phase II data, at which point they are positioned for sale to pharma at values reflecting market potential and probability of success.

Our total investment to bring a program to this point is about US$15 million to US$20 million. This is significantly less than what a typical company would spend to reach this stage, for several reasons. The initial investments in each asset are very small, and we don't waste money on overhead at an early stage. Since we don't build companies with multiple pipeline assets, each drug candidate is assessed on its own merits, and management has no incentive to keep an unworthy project alive just to "save" the company. To the contrary, project managers are secure in the knowledge that they will be recycled to work on the next pipeline asset if a project fails.

The example of PanGenetics, a company in Index Ventures' asset-centric portfolio, validates the ability of our model to generate strong returns. *Start-Up* magazine recently cited the November 2009 sale of one of PanGenetics' two antibodies, anti-NGF PG110, to Abbott for US$170 million as the largest down payment ever for a Phase I project. PanGenetics was created in 2005 with €36 million (US$50 million) from Index and a small syndicate of other investors and run by Kevin Johnson, former Chief Technology Officer of Cambridge Antibody Technology. The company, which had two early-stage antibody assets from the start, was actually run and legally structured as two separate businesses, PanGenetics 1 and PanGenetics 2. With the NGF asset sold and returns from PanGenetics 1 returned to investors, PanGenetics 2 still has its asset in development.

Lessons for the new normal

Our industry is at a point in its evolution when we have limited resources and large unmet needs. More than ever, it is important for us to focus on what those needs are and how they can best be met. For patients, the critical need is drugs, not companies. For investors, the need of the day is more efficient deployment of capital and quicker paths to value inflection points. The most effective way to meet this need is for investors to think of portfolios as numbers of assets rather than companies. An asset-centric funding model has never been more relevant. ▶

In both of these models, investors are also getting around the "you-can't-build-it-to-sell-it" problem more effectively than they could under the traditional funding model. For one, while they are still looking for an exit via sale, they aren't building very much – project-funding approaches inherently involve less infrastructure and overhead. In addition, since these projects involve very specific propositions (taking a particular asset to a defined development threshold in a short period of time), investors are typically able to validate at the outset buyers' interest in purchasing them if they succeed, and can even effectively hold the auction "up front" through the negotiation of a purchase option.

Other approaches have similarly involved trying to find ways to fail fast. As has been widely reported, Lilly's Chorus experiment has successfully done this within one large pharma company by developing a leaner way to get to clinical proof of concept. That same approach is now being used in a wider way through a venture-backed start-up, Flexion Therapeutics. Flexion, founded in 2007 by the founding members of Lilly's Chorus division with backing from Versant Ventures, 5AM Ventures, Sofinnova Partners and Pfizer, in-licenses molecules from big pharma companies where it thinks it can quickly and cheaply get them to proof of concept. (For more details, see "Lean proof of concept," by Michael Clayman, on page 9.)

Big pharma

Big pharma is facing its own new normal, though this has less to do with the Great Recession than with longer-term trends that preceded the economic downturn. Specifically, the industry's patent cliff, and the fact that most firms do not have enough in their clinical pipelines to replenish the revenues they are poised to lose, have driven aggressive restructuring measures and efforts to access innovation externally. There are differences of opinion on the need for diversification – some companies are remaining focused on the core business of drug innovation, while others are expanding into a variety of other businesses, from branded generics to nutraceuticals. Despite these differences, the industry has consistently been shifting from a blockbuster-based model toward one based on products targeted at smaller patient populations. These changes, sometimes referred to as the transition from Pharma 1.0 ("the blockbuster model") to Pharma 2.0, have been discussed extensively, including in prior editions of *Beyond borders* and in our sister publication on the pharmaceutical industry, *Progressions*. For several years, the biotech industry benefited from big pharma's pipeline challenges, as large companies bid up prices for desirable platforms and late-stage pipeline assets.

While pharma's patent cliff has been anticipated for some time now, the pressures are becoming particularly acute just as biotech and pharma companies are grappling with the new normal. For several pharma companies, the biggest blockbusters are scheduled to go off-patent in 2011 and 2012, at which point the industry will finally be on the other side of the cliff, leaving a number of firms with reduced revenues and cash flows with which to buy their way out of trouble.

Pharma's challenges are also being compounded by the transition to the next phase of the industry – something we term "Pharma 3.0" in the 2010 edition of *Progressions*. The convergence of new trends such as health care reform and the adoption of health information technology (IT) promises to change the very business that drug companies are in, from selling drugs to delivering outcomes. As pharma companies desire new solutions to deliver health outcomes – as well as to address Pharma 2.0 challenges such as serving patients in emerging markets – many "non-traditional" companies are sensing opportunities to capitalize on increased health spending and are entering the fray. Pharma companies are beginning to collaborate with these entrants – from sectors as disparate as IT, telecommunications, retail trade and financial services – to create entirely new service and product offerings customized for the world of Pharma 3.0. We've seen a flurry of partnerships in recent months, and while these have mostly been early-stage experiments and pilot programs, partnering with non-traditional entrants will likely become a greater focus over time.

Pharma companies have long been vital partners for the biotechnology industry – providing everything from clinical expertise to R&D funding and from validation of early-stage assets to exits for investors and founders. It is almost inevitable, therefore, that the sweeping changes under way in the pharma industry will have significant repercussions for biotech companies and their investors.

For instance, there has been a marked uptick over the last couple of years in the number of deals that are structured to include options. In these transactions, buyers do not purchase or in-license an asset but rather pay for the right to license it at a later date (e.g., when a clinical trial has been successfully completed). To some extent, these deal structures, which typically allow buyers to take on less product development risk, have been enabled by the fact that many biotechs have seen their bargaining power diminish in today's capital-constrained environment. But option-based transactions are also being

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Michael Clayman
Flexion Therapeutics
CEO

Perspectives for the new normal

Lean proof of concept

Drug R&D is an imperfect science. Moving from discovery to clinical proof of concept is typically expensive and time consuming. Companies often have to de-prioritize molecules simply because they don't have the resources to pursue all their Phase I or Phase II assets. These decisions are often based on preclinical data, which is logical. Unfortunately, preclinical data is rarely predictive of what one finds in the clinic, and companies have often been surprised later. Promising molecules have failed in late clinical trials, while molecules that were considered low priority based on preclinical data have gone on to generate positive results downstream.

Lean proof of concept

In 2001–02, when Neil Bodick and I were at Eli Lilly, we launched Lilly's Chorus group based on Neil's idea for a lean proof-of-concept clinical-development accelerator. This new division was created to bring molecules from discovery labs to meaningful clinical proof of concept in a lean manner. Specifically, our goal was to improve the probability of launch by at least 20 percentage points in less than 24 months and at a cost of less than US$5 million.

We did not follow the typical path to proof of concept — using very small studies that are poorly controlled and rely on unvalidated endpoints to give some suggestion of efficacy. Instead, we designed well-controlled studies to derive truly meaningful data using validated surrogates or bona fide clinical endpoints. We intentionally focused only on that work which was required to safely progress the molecule to meaningful proof of concept. Our strategy was to only do registration work for molecules that delivered good proof-of-concept data.

Lilly would offer molecules to us when they had insufficient resources to advance them within their R&D organization. If we thought the indication lent itself to the Chorus approach, we took it in with the idea that when we reached proof of concept, the molecule would "graduate" from Chorus back to the larger organization.

Chorus ultimately grew to a 22-person team. During our time there, we worked on 19 molecules — nine of which we advanced to proof of concept, including four with positive data. Two of these four were very big surprises, where the larger organization had partially or completely given up on the molecules but our data advanced them to the top of the priority list.

Flexion: the next act

In November 2007, Neil and I formed a new start-up around this approach — Flexion Therapeutics — with the backing of Versant Ventures. Flexion in-licenses molecules that have been de-prioritized by big pharma companies. Our goal is to get these assets to proof-of-concept value inflection points so that big pharma acquires the asset, or perhaps even the entire company. We like to in-license a small basket of assets from a company — perhaps three molecules, one of which the pharma company can bring back into its portfolio if Flexion generates positive proof-of-concept data.

Our due diligence includes areas we didn't have to worry about at Chorus, such as target validation, potential downstream safety problems and commercial potential. Since pharma companies have become more demanding — wanting data that is even further downstream than clinical proof of concept — our strategy includes the possibility of a specialty pharma approach where we carry the molecule further, even including commercialization. Out of our current portfolio of four molecules, two in particular lend themselves to being such specialty pharma plays.

Lessons for the new normal

I often get asked for the recipe of our "secret sauce" for demonstrating proof of concept for US$5 million in less than 24 months. Well, there's nothing secret about it. You need a certain amount of experience, but there are lots of experienced people in our industry. You also need a passion for doing bold, killer experiments in the leanest possible way within lean organizations. Perhaps the secret is that the sum of those elements is an uncommon combination.

But it's no secret that we need more efficient drug development in today's market. At big pharma, discovery output currently outstrips development capacity, and many companies are entirely exiting certain therapeutic areas — creating new opportunities around these assets. Meanwhile, biotech companies and investors face a tighter capital environment and need to conduct R&D more efficiently. The need for a lean proof of concept has never been greater. ►

"For most of the history of the biotech industry, licensing between pharma and biotech companies has largely flowed in one direction — from biotech to pharma. But things may now be poised for change."

driven by pharma companies' constraints, as buyers are looking for ways to get more "shots on goal" with smaller R&D budgets. Big pharma companies that were active users of options-based transactions in 2009 included GlaxoSmithKline (in deals with Vernalis, Prosensa, Chroma Therapeutics, Supergen, Concert Pharmaceuticals and others) and Novartis (in deals with Proteon and Elixir Pharmaceuticals). The structure was also popular with large biotechnology companies, including Cephalon. (For more on these transactions, refer to the *Deals* article in this year's *Beyond borders*.) In the new normal, biotech companies can expect more large buyers looking to construct deals using such options-based structures.

In the challenging funding environment of the new normal, big pharma is more important than ever as a source of capital for biotech companies. But to succeed in partnering with pharma, biotech firms will need to actively track the changes taking place in the pharma industry. For instance, the recent wave of pharma-pharma mega-mergers — coupled with pharma companies' initiatives to assess strategic priorities and exit entire lines of business — has reduced the number of potential buyers for any given asset. In addition, as pharma companies grapple with the challenges of Pharma 3.0, they will increasingly need to partner with non-traditional players from a host of other industries.

In recent years, as pharma companies have competed aggressively to license the most promising assets from biotech firms, many large firms have taken to describing themselves as the "partner of choice" for biotech — highlighting their positive attributes for potential biotech partners. In the new normal, biotech companies may instead need to ensure that they are the partners of choice for pharma. To do so, they may need to design their development efforts with buyers in mind and track shifts in pharma companies' strategic priorities over time.

But the changes under way in big pharma will also create many opportunities for biotech companies. Some of the biggest openings may be in the area of licensing. For most of the history of the biotech industry, licensing between pharma and biotech companies has largely flowed in one direction — from biotech to pharma. But things may now be poised for change. As discussed above, many pharma companies are narrowing their therapeutic focus and will have less financial wherewithal to pursue everything in their labs in the years ahead. It is very likely that companies will out-license assets that they are unable or unwilling to develop internally. Pharma companies have sometimes been risk-averse in their attitudes toward out-licensing — preferring to hold on to something rather than give away the next big thing to a competitor. But now, with companies deciding that it is no longer strategic for them to compete in certain spaces, pharma managers may be less reticent. This could create opportunities for investors that can pair promising clinical candidates with experienced entrepreneurial teams to commercialize these assets.

The out-licensing trend will get an additional boost from the need to boost R&D efficiency. As a bottom-line focus further constrains research budgets, pharma companies will need to fundamentally revisit the cost-benefit of their R&D expenditures and search intensely for the most efficient means of pursuing their product development goals. As they do so, it is quite likely that some firms will see more efficiencies and higher returns from conducting a greater share of R&D — particularly in discovery and early clinical trials — in concert with external partners. In January 2010, a widely read research report by Morgan Stanley, *Pharmaceuticals: Exit Research and Create Value*, argued that pharma companies could earn better returns by reducing their reliance on internal research.

The wave of out-licensing will also create opportunities for investors and biotech entrepreneurs, spawning new start-ups and creative business models. It is not surprising that Michael Clayman explicitly addresses the opportunities latent in pharma's move to exit therapeutic areas when discussing Flexion's growth potential.

This trend will be boosted by the growth of "open innovation" approaches. As big pharma companies look to do things more efficiently, they are moving well beyond the historic "not invented here" mentality to collaborate in new, increasingly open ways. In recent years, we have seen companies

partnering in the pre-competitive space, for instance, where it makes sense to pool resources and tackle early-stage scientific challenges. One prominent example, Enlight Biosciences, is discussed in some detail in last year's *Beyond borders*. Eli Lilly has launched its PD^2 initiative to attract early intellectual property (IP) from academia. In 2009, we also saw GlaxoSmithKline open much of its IP portfolio in neglected diseases and invite other companies to follow suit (as Alnylam did in July 2009). We don't expect such open innovation approaches to account for the vast majority of biopharmaceutical R&D, but it will be an important presence in certain niche areas — primarily in early research and preclinical development.

Payors and governments

In recent years, biotech and pharma companies have faced growing pricing pressure from governments and private-sector payors. The drivers of this trend — rapidly growing health care costs, the desire to expand access to a greater percentage of the citizenry and aging populations — continue unabated, and as a result, pricing pressures are expected only to grow over time.

The global recession has further increased the budgetary pressures on governments. Tax revenues have plummeted with the downturn in economic activity, while policy-makers have had to boost spending on stimulus packages and unemployment benefits. In the US market, where health insurance coverage is largely tied to employment status, widespread layoffs have dramatically increased the number of people at risk of losing access to health care.

Meanwhile, the rules of the game are changing. Over the last year, significant health care reforms have been introduced in some key pharmaceutical markets, the most prominent among which are the US and China. These reform measures — which promise over time to redraw the competitive landscape, revise rules and regulations and reorder economic incentives — are largely attempts to find more sustainable ways of providing health care in response to the pressures mentioned above. Not surprisingly, similar measures are being considered or enacted across a number of other major developing markets as well, from Brazil to Russia to India.

Sweeping changes to health care systems will, almost inevitably, create new opportunities and challenges for biotech and pharma companies. (See *A closer look* on the next page for more on the implications of the recently passed US legislation.) One of the biggest challenges may come from the increased adoption of comparative effectiveness measures. The fact that many health care reform efforts need to reconcile two somewhat contradictory goals — expanding access to health care while containing costs — will require increased efficiency across the health care ecosystem and will likely increase the adoption of comparative-effectiveness regimes.

While they have become fairly commonplace in some European markets, comparative-effectiveness systems — in which reimbursement decisions are based not just on the efficacy of a particular treatment but on the incremental benefit it provides relative to cost — have been largely absent from the US health care system. That may not change dramatically in the immediate future; while the new US legislation provides funding for comparative-effectiveness research, it also explicitly prohibits government payors from making coverage decisions based on the findings. Still, the provision is widely viewed as potentially setting the stage for wider use of comparative-effectiveness findings in the US market going forward. Meanwhile, the significant increase in coverage under the new law will only increase the need to control costs — making the future adoption of comparative-effectiveness considerations ever more likely. To some extent, the moveto comparative effectiveness is likely to proceed regardless of the actions of government payors. The increased use of health IT, for instance, will permit anyone with access to significant volumes of data — hospital systems, insurance companies and others — to use data mining to identify which patient populations a certain treatment is most effective on. (For examples of such initiatives, see the 2010 issue of *Progressions*.)

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"The fact that many health care reform efforts need to reconcile two somewhat contradictory goals — expanding access to health care while containing costs — will require increased efficiency across the health care ecosystem and will likely increasing the adoption of comparative-effectiveness regimes."

A closer look

Connie Austin
Ernst & Young LLP

Reforming US health care

In March 2010, after many months of debate and controversy, health care reform legislation was finally enacted in the United States. The legislation — which aims to expand access to health care and boost efficiency in spending and delivery — promises over time to transform the US health care ecosystem.

While final determination of how certain provisions are to be implemented will play out in the months and years ahead, it is clear that life sciences companies will soon face a significantly reshaped competitive landscape as a result of the legislation. While pharmaceutical and medical device companies will be significantly affected, the impact on the biotechnology industry depends on a company's stage of development. Large, commercial-stage enterprises will be more impacted by some of the funding mechanisms discussed below, while emerging, R&D-stage enterprises may benefit from R&D funding provisions included in the final law. Like companies in all industries, large biotech companies will also be affected by changes related to employment-based health insurance coverage.

One of the primary goals of health care reform — expanded access to coverage — will be realized through a series of policy changes which will be implemented starting in 2014. These provisions include mandates requiring individuals to buy and maintain health care coverage and requiring most employers to either offer and contribute a minimum amount toward coverage for their employees or pay a new per-employee fee.

The increased insurance coverage will boost demand for drugs. However, the increase in volume will be partially or wholly offset by changes in payment mechanisms and levels, driven by increased coverage under Medicaid. The program is partially funded by an increase in Medicaid drug rebates and new annual fees and excise taxes on drug manufacturers and medical device companies. The impact on any individual manufacturer will depend on its product mix and whether expanded sales to previously uncovered patients will offset higher taxes and rebates. The potential returns on pipeline investments will be impacted by higher rebates. There is also a timing mismatch, since increased coverage will not be implemented for several years, while companies will see higher costs much sooner.

Biotechnology companies will benefit from a biosimilars provision that gives new biologics a 12-year period of data exclusivity before they face direct competition. However, the FDA will still need to provide guidance to establish an abbreviated regulatory pathway for biosimilars. The final legislation also excluded two provisions that the industry had been concerned about: allowing US consumers to import drugs from abroad and letting the federal government negotiate drug prices directly with manufacturers.

The increase in health care coverage creates new opportunities and challenges for companies. The real opportunity, though, is for companies to tailor their business models, processes and infrastructures to the needs of the new normal, where there will be increased focus on health outcomes.

Over the last few years, we have seen some creative new responses to these pricing pressures. In 2007, Janssen-Cilag (a Johnson & Johnson company) obtained coverage for its cancer drug Velcade in the UK only after it agreed to provide what amounted to a money-back guarantee to the payor. The company agreed to reimburse UK's National Health Service for the cost of treating patients that did not respond well to the drug. Since then, we've seen a number of other outcomes-based pricing arrangements emerge. (For a detailed discussion of these arrangements, refer to the *Products and pipeline* article, "Steady growth.")

The picture that emerges from these changes is one of a new normal in which biotech executives must contend with increased risk and uncertainty. Mounting pricing pressures — exacerbated by the economic downturn, which has squeezed payors' budgets — will accelerate the move toward comparative effectiveness regimes. Creative pricing models, such as the outcomes-based approaches that have become increasingly common in recent years, may be the shape of things to come.

Companies have traditionally viewed marketing approval as the finish line on the long relay race to product approval. In today's market, however, that finish line has been moved further back. It is no longer sufficient to demonstrate safety and efficacy, since companies must cross additional hurdles to obtain reimbursement for their products. These considerations are being taken into account in deals, where buyers and licensors are looking not just at the scientific merits of a product but also at the likelihood that it will be reimbursed at an attractive price point. Milestones in strategic alliances — long tied to clinical-trial outcomes — now often include the achievement of commercial targets as well.

Biotech companies will need to consider these issues earlier and earlier in their development efforts. We are likely to see more dialog between companies and payors regarding the potential reimbursement of drugs in the pipeline. This interaction will become increasingly important when making decisions about which assets to take forward and in partnering and M&A discussions.

Beyond growing reimbursement risks, however, companies also face an inherently uncertain policy and regulatory environment. The rules, as we discussed above, are changing in sweeping and often unpredictable ways. The changes under way as part of China's health care reform package (discussed in the *China* article) will have tremendous implications for which products are covered and how they are paid for, and companies will need to track these shifts. In the US market, after operating under a cloud of uncertainty for more than a year as the often-chaotic health care reform debate lurched through Congress, companies face continuing uncertainty ahead as the legislation will likely face a gauntlet of legal challenges and efforts to pare it back.

Biotechnology companies

Despite tremendously exciting new technologies and approaches, the world's longest relay race isn't getting any shorter. Developing drugs is still an exceedingly expensive and highly time-consuming endeavor. In the capital-constrained realities of the new normal, the question is whether biotech companies will be able to access the amounts of capital required and whether we will see solutions emerge that will allow firms to go the distance and mature into large organizations with commercialized products.

Traditionally, biotech companies have relied on three principal sources of funding: venture capitalists, public investors and alliances with pharma companies. Unfortunately, raising money from each one of these sources has become more problematic in today's market environment.

As discussed above, companies looking to raise **venture capital** face a higher bar as VCs have become more selective. At a time when exits are scarce, investors are having to retain capital to sustain existing portfolio companies. And as the supply of capital from limited partners has diminished, some VCs have not been able to raise the sorts of funds that we have seen in recent years. With fewer dollars chasing every opportunity, company valuations will become more muted. To the extent that VCs adopt asset-based funding approaches such as the one used by Index Ventures, we can expect to see a smaller share of total funding allocated to starting new companies.

Meanwhile, the **public markets** have continued to pump healthy amounts of capital into the biotech industry, but these sums have largely gone to established public companies looking for additional capital. There has been very little available for smaller companies looking to raise public equity for the first time. IPO investors are also more selective and are seeking opportunities where the development has progressed far enough to remove some of the R&D risk. Even in those opportunities, recent deals have priced below the expectations of companies and their investment bankers, and we don't anticipate a broad change in investor sentiment in this regard.

With access to venture capital and public markets relatively limited, this leaves the third traditional biotech funders, **pharmaceutical companies**. While big

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Perspectives for the new normal

Edward Lanphier
Sangamo BioSciences
CEO

Focus and leverage

Sangamo BioSciences was founded in 1995, a time when biotech funding was very scarce. But with focus and a business model that leverages existing activities and assets, our company thrived through the depths of this challenging period – and beyond.

Validation without dilution

How were we able to do this? In a difficult funding environment, we focused early on raising non-dilutive financing and validating our technology for potential investors. Soon after our founding, for instance, we obtained a US$2 million Advanced Technology Program grant. This investment was non-dilutive, had no strings attached and – since it came from a very competitive program – was highly validating. The money could be applied to develop our core technology and, unlike our Small Business Innovation Research (SBIR) grants, was a material amount. In 1997, we did a Series B financing with two high-profile, experienced investors – Lombard Odier and JAFCO – which provided further validation.

Over the next couple of years, we entered more than a dozen research tools/functional genomics deals with pharma companies. These were very small, often unfunded, transactions. They involved no intellectual property (IP) transfer. We simply used our zinc finger DNA-binding protein (ZFP) technology to create unique reagents for our partners' needs. But since these were deals with big pharma partners, they were validating for investors.

In late 1999, soon after our US$9 million Series C round, the markets turned bullish for biotech stocks. We announced our first therapeutics partnership, with Edwards Lifesciences, at the Hambrecht & Quist Healthcare Conference in January 2000. Boosted by this validating partnership and overall market sentiment, we successfully raised US$52.5 million in our April 2000 IPO (10 years ago!).

Focus and leverage

We monetized our core technology to earn revenues while also focusing on developing therapeutics. The broad applicability of our technology – engineering ZFPs that can target and affect essentially any DNA sequence – allowed us to do deals very efficiently, since we could leverage the same technology with few additional resources and generate ZFPs for many different targets. Our ability to monetize our technology was further enhanced by obtaining exclusive licenses to key academic IP portfolios and investing in our internally generated patents, thus providing exclusivity to our partners.

In a resource-limited environment, we focused, prioritized and leveraged our strengths in several ways. First, we have always invested aggressively in our core technology. Second, we've prioritized our own therapeutic development programs in areas where our technology provides differential technical advantages. Third, we've simultaneously partnered in areas outside our core therapeutics focus, such as plant agriculture, transgenic animal models and cell-line engineering. In the plant space, for instance, we executed an agreement with Dow AgroSciences that leveraged each party's core competencies. This allowed us to leverage the work we were already doing and let Dow pursue development issues that are unique to plants.

Through license fees, milestones and sublicense payments from deals such as those with Dow and Sigma-Aldrich – as well as our cell-engineering deals with Pfizer and Genentech and support from disease foundations – we have received more than US$75 million in payments which we have used to advance our therapeutic programs. These revenues have partially offset our development costs so that our operating cash burn has never exceeded US$20 million, even as we've conducted four Phase II trials and advanced two other therapeutic programs into the clinic. These partnership revenues have even allowed us to grow during downturns. At a time of industry layoffs, we increased our head count in 2009.

Today, we have completed four Phase II trials in our lead program, started a 150-patient Phase IIb trial and initiated three Phase I trials in HIV and cancer. We own 100% of our therapeutic platform and have retained significant downstream value in our partnered programs in non-therapeutic areas. And by focusing and leveraging our core technology, we've remained relatively lean, with only 85 employees.

Lessons for the new normal

This basic strategy could be applicable in today's difficult funding environment. Venture investors have little appetite for higher-risk investments and public markets seem willing to back only very mature firms. But companies also have a wider range of non-dilutive funding options – not only government grants but a growing number of foundations focused on a specific disease. And while Sangamo's technology and IP platform is exceptionally suited for breadth, many companies have technologies that could be leveraged in non-core areas or through targeted arrangements with pharma companies. Staying lean and focused at a time of constrained capital has been a reality for Sangamo since the beginning, and our model has served us well through multiple funding cycles. ▶

pharma's need for pipeline assets is as acute as ever — indeed it becomes more urgent by the day — biotech companies face a more challenging reality here as well. The recent wave of pharma consolidation and efforts by pharma companies to exit certain therapeutic categories have effectively reduced the number of potential buyers for any given asset. In addition, biotech companies will over time be competing with companies from other industries for the attention of pharma partners as pharma moves into new lines of business.

So what options do companies have in the current environment? While there are no easy answers, and companies will need to determine the best way forward based on their individual circumstances, salvation may lie in what this industry has always relied on in difficult times: harnessing its creativity.

The first arena in which companies will need to be creative is fund-raising. The article by Edward Lanphier of Sangamo BioSciences on page 14 provides an instructive case study. Sangamo has survived a number of downturns since the company's formation in 1995 by not just tapping venture capital but also creatively using grants from disease foundations and government programs. In addition, the company entered into service agreements and non-exclusive licensing transactions to offset some of its early R&D costs while advancing its core technology. Today, companies have a wide range of non-traditional funding options as long as they are willing to look broadly and think creatively. There are a growing number of disease foundations with targeted funds available. The article by Ron Xavier on page 74 highlights funding options arising from government economic incentive programs. As we go to press, there is considerable media coverage of the new Qualifying Therapeutic Discovery Project Credit in the recently passed US health care reform law. It is widely anticipated that many US biotech companies will be able to access the credit, given the expansively defined cost categories that can qualify.

"Working with third parties is not just about slashing costs. More importantly, the opportunity is to work with partners that can have a differential impact on the efficiency of a company's drug development."

Beyond broadening the search for capital, companies will also need to deploy the capital they do have more efficiently. In the current environment, of course, companies have been slashing costs aggressively. Using capital efficiently will require firms to prioritize R&D programs. In some cases, a company with platforms or other leverageable assets may be able to partner in areas outside its core therapeutic focus. And firms will need to assess which activities they should conduct internally and which ones should be conducted by third parties.

Working with third parties is not just about slashing costs. More importantly, the opportunity is to work with partners that can have a differential impact on the efficiency of a company's drug development. In last year's *Beyond borders*, Samantha Du of China-based Hutchison MediPharma argued that partnering with Chinese companies gives Western firms distinct advantages because Chinese firms tend to be much more integrated across various disciplines and capabilities than is the norm in the US or Europe. In his article in this year's report, Werner Lanthaler of Germany-based Evotec argues that the services his company offers allow biotech R&D projects to reach critical go/no-go decision points more quickly — enabling the most promising ones to move forward and compelling the others to fail fast.

As discussed above, biotech companies will need to work harder to attract the attention of big pharma partners — many of which may be distracted by mega-mergers or less interested in certain assets because of changes in strategy or market dynamics. A number of the *Perspectives for the new normal* that accompany this article highlight creative approaches to partnering with big pharma. Leonard Schleifer of Regeneron Pharmaceuticals, for instance, describes his firm's collaboration with sanofi-aventis. This deal structure — a 10-year alliance that gives Regeneron a steady flow of funding and gives sanofi-aventis a steady stream of targets which it can opt to co-develop — is very attractive in the current environment. (Regeneron is not alone in using such a structure. Writing in last year's *Beyond borders*, Adelene Perkins of Infinity Pharmaceuticals described a similar long-term arrangement with a deep-pocketed partner.) Such deals free biotech companies from having to worry about continuously raising capital and allow them to adapt pipeline decisions based on changing conditions. The steady source of capital from a deep-pocketed partner also gives biotech companies the ability to build a much bigger pipeline than is the norm for most emerging biotech companies.

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Leonard Schleifer, MD, PhD
Regeneron Pharmaceuticals
CEO

Perspectives for the new normal

Succeeding together

Biotech and pharma companies have been partnering for decades, and people have been looking for the perfect pharma-biotech alliance structure for about as long. How do you truly maximize the strengths of each partner – biotech firms' entrepreneurship, nimbleness and research innovation and pharma companies' financial, development and global marketing capabilities – without quashing what they do best?

Many people would say that the closest the industry has come to a "perfect" formula is the original Roche-Genentech relationship, where Roche invested significant resources in Genentech but also gave it tremendous independence. Although that relationship was enormously productive and mutually beneficial, that structure has been relatively rare in our industry. For a big pharma to invest more than US$1 billion in a small company requires confidence in the company's ability to deliver. And many small companies don't fully appreciate how valuable big partners can be.

Regeneron's collaboration with sanofi-aventis to discover, develop and commercialize fully human monoclonal antibodies shares some elements with the Roche-Genentech alliance, and our experience may be instructive for other companies. Our collaboration first grew out of a 2003 alliance to develop a vascular endothelial growth factor (VEGF) trap for cancer. In 2007, sanofi-aventis decided to expand its biotechnology presence, and – since we knew by then that we worked well together and had confidence in each other – we agreed to a new, five-year antibody collaboration. The deal terms provided that we would get about US$100 million a year for preclinical research on human monoclonal antibodies for a variety of targets. As the fruits of this research are ready to move into clinical trials, sanofi-aventis has the right to opt in to the co-development of the antibodies. Sanofi-aventis then generally funds all the development costs and we repay 50% of those costs out of our share of future profits. When products are commercialized, we are entitled to 50% of US profits and 35%–45% of non-US profits.

In 2009, after Chris Viehbacher became CEO, sanofi-aventis reviewed its relationships. By the end of 2009, we had already delivered on our original promise by putting five antibodies into clinical development in the first two years of the agreement. So sanofi-aventis proposed that we expand and extend our collaboration: they would provide us up to US$160 million a year for preclinical research, the funding would stretch out for 10 years (through 2017), instead of the original five, and we would aim to advance an average of four to five antibodies into clinical development each year.

This arrangement provides valuable stability because we can count on steady inflows of significant funding for the next eight years. This allows us to make the long-term investment in people and research and manufacturing infrastructure required to meet our commitments to sanofi-aventis. If we sustain the success rate we've had so far, we would move 32 to 40 candidates into clinical trials through this collaboration. Of course, building a pipeline that large – something only the biggest biotech companies can even dream of – is very expensive, but we have pre-negotiated funding for the enormous development program. By entering into one large collaboration rather than doing individual deals with several partners, we minimize the cost of executing and managing those relationships, as well as the complexity of joint governance. Importantly, we retain control over our discovery efforts, including which programs to prioritize. We also maintain an independent culture – Chris Viehbacher and I have no intention of "sanofizing" Regeneron. On the other hand, sanofi-aventis will take the lead and have the final say in commercialization decisions, where they have extensive expertise, experience and resources.

Lessons for the new normal

What lessons are there for firms considering Regeneron's approach? First, companies will need to develop proprietary and scalable assets (the *VelocImmune*® antibody technology platform, in our case) that allow them to leverage capabilities broadly. But it's not just about selling a platform. We also hired world-class scientists and invested in managing and continually improving our platform.

To find a partner willing to make a significant long-term commitment with an equitable sharing of decision-making, biotech firms will need to build mutual trust. Deal structure can help further align interests. While people talk about "win-win" deals, this is often really about trying to win while convincing the other side that they are going to win, i.e., "win-lose." In our case, Regeneron can only succeed if sanofi-aventis succeeds, and vice-versa. That's important, because now more than ever, we need successes – not just for companies and investors, but for the patients we ultimately serve. ▶

John Maraganore
Alnylam Pharmaceuticals
CEO

Efficiency and leverage

Alliances between biotech and pharma companies are ubiquitous in our industry. While there have been thousands of deals — and deal structures — over the years, the vast majority of structures fall into one of two categories: collaborations in which biotech companies provide research or other services, and licensing transactions in which pharma companies in-license intellectual property (IP) for use on an exclusive basis in specific therapeutic areas or targets. At Alnylam, we have instead opened up a third path, one that is relatively rare: licensing our platform on a *non-exclusive* basis to multiple partners, including Novartis, Roche and Takeda.

How did we succeed in pursuing this approach? We benefited from a platform that is broadly applicable to different targets and therapeutic areas — small interfering RNAs that can target any gene. But our success was really enabled by our focus on consolidating IP around our platform. This is rare in an industry in which the IP related to many key technologies — monoclonal antibodies, for instance — is highly fragmented. By consolidating IP, we have been able to empower our partners with an uncommonly comprehensive suite of capabilities. For instance, we gave Roche access to Alnylam's capabilities and also transferred a large number of procedures and protocols. With Takeda, we transferred most of our technologies so they knew how to use our approaches and methods. Importantly, we still retain the ability to get the upside benefits seen in more typical collaborations, including milestone-based royalties from our partners' efforts. With Takeda, we even have the option to co-develop and co-promote products that they commercialize in the US.

Efficiency and leverage

This approach has given us greater efficiency and leverage. With such a broad-based platform, we would be limited by our own resources if we pursued targets using a more conventional approach. Instead, with non-exclusive licensing, we are leveraging the capabilities and resources of our partners. Our R&D investment through alliances is several orders of magnitude larger than our internal pipeline R&D spend. Not only do these deals bring in revenue to fund our core activities — we've raised more than US$675 million to date from partnerships — but we also retain a stake in the upside from our partners' efforts.

If we had instead done a series of exclusive deals, we would likely have faced challenges around management workflow, resource allocation and potentially diverging interests. And to conduct R&D internally with pharma funding, we would have had to add significant resources, which can reduce efficiency and create problems around transitioning those people when alliances are dissolved.

While we could, in theory, enable companies to become our competitors down the road (we don't, for example, prevent them from targeting genes we're focusing on) it is remarkable how very little intersection there has been so far on the targets we are pursuing. Targets, like beauty, are in the eye of the beholder.

Lessons for the new normal

How replicable is our model? While not all firms will be able to use this approach, there are other exciting platforms where stories similar to Alnylam could be born. Several platform companies are looking at our partnering model.

Companies considering a non-exclusive model need to start by consolidating IP, which is what we focused on for our first 6 to 12 months. Already, other platforms with IP are relatively consolidated — for instance, aptamer platforms and stable-peptide platforms. But consolidation doesn't have to be focused on a technology; companies could consolidate IP around a swath of biology instead.

Companies will need to focus next on validating their technologies. At this stage, pragmatism will typically require exclusive licenses, as in our early, highly validating alliance with Merck. Companies should define clear boundaries about what's in and what's out of the alliance, so that they are not prohibited from doing broader, non-exclusive deals down the road. Finally, it is critical to continually invest in improving the platform over time. We still spend about 40% of our internal R&D on enhancing our platform.

With these guiding principles, I fully expect that other companies will be able to use non-exclusive licensing. Our approach is ultimately about extracting the most value from a valuable asset by leveraging the strengths of others — a relevant principle in today's trying times. ▶

John Maraganore of Alnylam Pharmaceuticals describes a very different deal structure. His company has been able to pull off something truly rare — it has simultaneously signed significant non-exclusive licensing deals with a number of pharmaceutical companies. These deals — which give Alnylam's partners access to the company's small interfering RNA platform — allow Alnylam to leverage its platform more broadly than it could have on its own, by harnessing the R&D efforts of its partners.

These two deal structures are in stark contrast to one another. Regeneron's deal involves going deep (a long-term relationship with one partner) while Alnylam has gone wide, striking non-exclusive deals with many partners. Yet, there are some common themes and lessons. The first is that both were enabled by having strong platforms. While not every biotech company is blessed with a compelling platform, companies looking to attract big pharma partners at attractive terms will need to focus on developing strong differentiating assets. Second, despite being so different, both deal structures appear to involve less distraction and more efficient resource allocation than a series of exclusive deals with multiple partners, since the companies are freed up from the operational challenges involved in managing alliances with several parties.

For companies looking for creative ways of partnering with pharma, though, some of the best opportunities may come from the fact that pharma companies need efficient solutions in the new normal as much as biotech companies do. Pharma's search for ways to increase the efficiency of its R&D spending — and the concomitant wave of out-licensing that may soon follow — could create tremendous openings for companies with creative solutions.

The responses and approaches we've discussed so far relate to the *business* of biotech — raising funds, operating efficiently, structuring deals. But biotechnology is ultimately a science-based business, and more efficient solutions could equally be found in scientific and technological advances. Indeed, this promise — radically efficient drug development, targeted therapies — has always been a big part of biotech's allure. Commercializing that promise takes time, and the tremendous advances in genomics and proteomics are only beginning to bear fruit. But game-changing developments — the rapidly approaching $1,000 genome sequence is frequently held up as an example — could very quickly boost market penetration and ignite investor interest.

Sometimes, business trends and scientific advances can reinforce each other. This could well be the case with personalized medicine, since many of realities of the new normal — the move toward comparative effectiveness and outcomes, the need for more efficient R&D — make the case for personalized-medicine approaches all the more compelling. To accelerate commercial adoption, there are challenges that will need to be worked through (the *Perspectives on personalized medicine* piece offers examples from seven industry leaders), but the near-universal need for more efficient health care solutions could well provide the impetus to overcome these barriers.

> "We can debate the semantics of old normals and new normals, but for this industry, dealing with challenges is the only normal it has ever known."

Guiding principles for the new normal

If there is a common theme defining the new normal, it is the search for efficiency. After the end of the era of "easy money," investors are looking for more efficient ways to fund innovation and achieve returns. Governments and payors have seen their budgets squeezed by the downturn and are demanding better outcomes for every health care dollar they spend. Facing imminent revenue declines due to looming patent expirations, pharma companies are focused on filling their pipelines — but are searching for ways to conduct R&D more efficiently than ever. And for biotech companies — looking to undertake the capital-intensive business of drug development in these capital-constricted times — the need for efficiency has never been greater.

How will each of these pressures shape the new normal? We don't know yet exactly what the new business climate will look like or how long it will last, but we can discern some likely trends. Access to capital will remain difficult for many, if not most, emerging companies. There will be a decline in the number of traditional start-ups funded by VCs and a corresponding increase in project- and asset-based funding. The number of public biotech companies will continue to fall, driven by acquisitions, market attrition and the lack of a robust IPO environment.

But economic dislocations, as we said at the outset of this article, produce winners and losers, and for every heightened challenge we've identified here, the new normal will also spawn new opportunities. Companies able to bring focus and creative thinking to the efficiency-related challenges of the new operating environment are the ones most likely to thrive from these opportunities.

To guide companies in these challenging times, we've identified five guiding principles for the new normal.

Seize funding opportunities. The era of easy money is over, and capital will be relatively scarce for some time. Broaden your search to include non-traditional (and non-dilutive) sources of funding. Be realistic – you may need to reset your valuation expectations for today's markets – and take funding when it is available.

Capital efficiency matters. To go the distance, you will need to use capital efficiently. Design studies and trials to fail faster. Prioritize the pipeline, using commercial as well as scientific indicators. Work with third parties – not just to cut costs but also to unleash operational efficiencies.

If you build it, will they pay? The finish line is not marketing approval but payor acceptance. It's never too early to think about reimbursement. Invest early in pharmacoeconomic analysis to inform R&D decisions.

Collaborate creatively. These are universally challenging times, and creative partnering structures can free you from turbulent public markets and help you go the distance.

Differentiate your asset. Creatively structured collaborations can help companies go the distance, but now there are fewer potential buyers, and they are more distracted and have fewer resources. To become a partner of choice, demonstrate what truly differentiates your product or platform.

Looking ahead

As we look to the year ahead, it is worth remembering what did *not* happen last year. The financial system and the global economy did not melt down. Most economists have been surprised by the speed of the recovery and now expect that their growth forecasts for the year were initially too pessimistic. The biotech industry has not seen the widespread bloodletting that many were expecting. Yes, things are different and they are more difficult, but many of the current challenges can also be viewed as intensified versions of impediments that biotech companies have been dealing with for some time now.

That may be the most salient point of all. We can debate the semantics of old normals and new normals, but for this industry, dealing with challenges is the only normal it has ever known. The biotech industry's resilience has always been based on innovation – in science and in business. Business adaptations always have, and always will, allow the most promising scientific breakthroughs to go the distance from idea to patient. ▶

Werner Lanthaler
Evotec AG
CEO

Perspectives for the new normal

There's gold in those efficiencies

In today's resource-constrained environment, drug development companies large and small are looking for more efficient ways to deploy capital and conduct R&D. Evotec may be able to offer some insights for these times, both because we have learned to leverage our assets better through the evolution of our own business model and because the model we have today enables more efficient resource allocation for us and our partners.

Panning for gold

While Evotec's platform technology – our high-throughput screening capability – has attracted capital and allowed us to endure, we have also altered our business model more than once because of changing market conditions. In the aftermath of the genomics bubble, the belief in the market was that gold lay in developing products rather than providing screening services. Consequently, in 2004, we changed our business model to focus on pipeline development. We acquired an early-stage pipeline in central nervous system and inflammation indications, with four to six clinical candidates. Unfortunately, we didn't find gold. Instead, as is often the case in our industry, we suffered clinical setbacks. And as is also often the case, the markets reacted severely, creating something of a crisis for our company.

It's worth remembering that in the original California gold rush, it was frequently not the people digging for gold who became rich, but rather the entrepreneurs providing *strategic* services to the gold diggers – Levi Strauss and others – who built sustainable, long-term, revenue-generating companies. The business model we adopted after our clinical setbacks reflects this reality. Today, our primary business is providing integrated and strategic outsourcing, essentially taking over R&D projects from our big pharma partners and developing them to designated clinical phases. This increases capital efficiency for our pharma partners, allowing them to "variablize" their fixed costs.

While we sacrifice some of the upside of discovering and developing our own drugs, from an operating standpoint, we are shielded from downside risk because we generate a steady revenue stream from our fee-for-service business. In addition, we gain potential upside from a much larger portfolio of projects through milestone payments and royalty streams from our strategic partners.

Lessons for the new normal

The biotech operating models we have seen so far have included much built-in inefficiency. Up till now, it has been permissible to build a 50-person company around a single target or idea from academia. Such companies have not had to worry much about overhead because the conventional wisdom has been that value in biotech is not created by cutting costs, but rather by spending on R&D.

But many of these inefficiencies will no longer be sustainable in today's "new normal." Financial investors are increasingly unwilling to build entire companies around binary, all-or-nothing clinical risks. And while big pharma is increasingly looking externally for innovation, the reality is that the vast majority of biotech companies will not be a good match for pharma buyers – they may be too unproven or their therapeutic or commercial focus may be unsuitable. For most companies, therefore, the answer will have to come from learning to do more with less.

Consequently, the drug development industry as a whole could benefit tremendously from a wider utilization of Evotec's approach. Our value proposition to our partners – give us your targets, and we'll bring them to a value-inflection point and get you to a go/no-go decision more quickly – is exactly what the industry needs more of. We need to see more companies unencumbered by large fixed costs and the pressures of constantly having to raise capital. We need to see more investors investing in portfolios of risks and funding them from one value step to the next – but not necessarily building a company around each risk.

We can no longer be wedded to the notion that there is only one way of doing things or that business models are built for eternity. To sustain biotech and sustain innovation, we need to challenge long-held ideas and seek new paths to efficiency. ▶

James Greenwood
Biotechnology Industry Organization
President and CEO

Biotech innovation and the role of public policy

The biotechnology industry faced extraordinary challenges over the last two years. But these challenges also highlighted the enduring strength of biotech innovation and the determination of our companies to develop products that heal, fuel and feed the world. If we can maintain and enhance public policies that support innovation, biotech will continue to fulfill its promise of offering powerful new solutions to some of the oldest human problems.

The global economic downturn froze access to capital markets that are a lifeline for this research-intensive industry. Many companies laid off workers, shelved or delayed research projects or, in the worst cases, shut down entirely. For others, the economic turmoil brought opportunities for strategic mergers or acquisitions.

Those that weathered the downturn have emerged leaner and more focused. Indeed, the biotechnology industry survived tough times before — to a large extent because of the tremendous value it adds in curing and preventing diseases, developing renewable energy sources and sustainable industrial processes and providing crops. Today, there are more than 250 approved biologic medicines and vaccines, with hundreds more in the pipeline. In 2009, 14 million farmers in 25 countries planted 134 million hectares of biotech crops. Industrial biotechnology supports a growing US$2.9 billion global market for industrial enzymes.

The science that drove these achievements remains strong. There were heartening signs in 2009, including the positive outcomes of clinical trials across several key areas and Food and Drug Administration (FDA) approvals of new products. Research in synthetic biology, gene therapy, bioinformatics, animal biotechnology and other fields shows the way toward whole new generations of biotech products.

But even as we cheer these scientific accomplishments and study economic data for signs of improvement, we must remember the role of public policy in advancing biotech innovation. We must ensure policy-makers understand the effects of their decisions. For instance, while they generally support developing new biologic treatments, policy-makers sometimes do not fully appreciate how expensive and high-risk biotech R&D really is. Public policies that maintain incentives for investors to back biotech innovation are therefore critical.

In the US, after months of debate, the President signed into law legislation that promises to transform significantly the nation's health care system. There are signs investor confidence in biotechnology has increased somewhat now that health care reform has been enacted. Although the full implications of the new law for the biotech industry remain to be seen, it does provide some resolution on several critical issues for the biotech community.

The new health care law includes needed provisions authorizing an approval pathway for biosimilars. The biosimilars language strikes a critical balance among promoting patient safety, expanding access, lowering costs and promoting continued innovation. It allows the original developer of a biologic to protect the proprietary data used to develop the medicine for at least 12 years. This preserves needed incentives for innovation law — and preserves hope for patients suffering from debilitating diseases who are still waiting for new treatments, preventions and cures.

With the legislative process concluded, the implementation of the new health care reform law — including the biosimilars and comparative-effectiveness research components — is now a top policy priority for the industry. Other priorities include: maintaining strong intellectual property (IP) protections; beginning negotiations with the FDA on reauthorization of the Prescription Drug User Fee Act; continued focus on improving the the FDA's performance; ensuring that the FDA receives appropriate funding; and adequately funding other agencies such as the National Institutes of Health and the Biomedical Advanced Research and Development Authority.

Promoting strong IP protection is also important internationally. Biotech companies depend on timely attainment and meaningful enforcement of patents and related rights. In today's global biotechnology industry, uniform and robust IP protection in all countries and regions of the world is critical. Recent trends in numerous countries undermine the IP protection essential for biotech innovation. This is an ongoing matter of concern for our industry.

Now more than ever, we need supportive policies to sustain biotechnology innovation and investment, so that the industry can continue to translate scientific discovery into useful products — and fulfill its promise to heal, fuel and feed the world. ▶

John Lechleiter, PhD
Eli Lilly and Company
Chairman, President and Chief Executive Officer

Using FIPNet to supercharge the innovation engine

The engine driving pharmaceutical innovation is broken. At a time when the world desperately needs more new medicines — for everything from influenza to Alzheimer's disease — our industry is taking too long, we're spending too much, and we're producing far too little. Ironically, this crisis comes at a time when we have vastly more scientific knowledge and data than ever before. But unless we change the way we do research, we won't translate this knowledge into advances for patients.

One of the key changes we're making at Lilly is transforming our fully integrated pharmaceutical *company* into a fully integrated pharmaceutical *network*, or FIPNet. In R&D, we're using FIPNet to build additional capacity and capabilities that leverage what we do well, while attracting molecules, funding and expertise from partners. Through FIPNet, we can greatly expand the pool of opportunity. We can share investment, risk and reward. And we can operate around the globe, and around the clock, to get work done more efficiently.

Our FIPNet activity in R&D can be grouped into three areas.

The first is **functional outsourcing**. Building on long experience with contract research organizations (CROs) in our clinical trials and toxicology work, we're developing new partnership models that provide us high-quality services at reduced costs with greater flexibility.

Consider two examples. In 2008, we sold our lab facilities and operations in Greenfield, Indiana, to Covance — a CRO with which we already had a FIPNet-style connection. As part of the transaction, we established a long-term relationship with Covance for work they perform for us in Greenfield. In China, rather than build our own chemistry facility, we partnered with a Chinese entrepreneur to develop ShangPharma, which provides exclusive chemistry services to Lilly.

The second broad area of our FIPNet is partnering around **novel ways to discover and develop molecules** beyond our traditional model.

In 2007, we signed a pioneering risk- and reward-sharing deal with India-based Nicholas Piramal, which develops molecules from our discovery pipeline up to the end of Phase 2, when we may opt to bring them back into our Lilly portfolio. Nicholas Piramal receives milestone payments — and a royalty if the product makes it to the market. We have similar risk-sharing arrangements for early-stage molecules with Suven Life Sciences in India and Hutchison MediPharma in China, as well as a relationship with TPG-Axon Capital for our two late-stage Alzheimer's disease molecules. [Editor's note: for more on Hutchison MediPharma's model, refer to "The dream of the sea turtles," by Samantha Du, CEO, in the 2009 edition of *Beyond borders*.]

Chorus, our virtual drug development network, is managing a steady state of 15 molecule programs with a dedicated staff of only 29 scientists. This cross-disciplinary group designs, interprets and oversees work through a network of organizations outside Lilly walls. Because of the lean development model, Chorus is able to reach proof of concept about 12 months earlier and at half the cost compared with the average of the current industry model. So far, Chorus has delivered data on 14 molecules, six of which resulted in positive proof-of-concept decisions, saving Lilly approximately US$100 million in the process. [Editor's note: for more on the Chorus approach, refer to "Lean proof of concept" on page 9, by Michael Clayman, CEO of Flexion Therapeutics.]

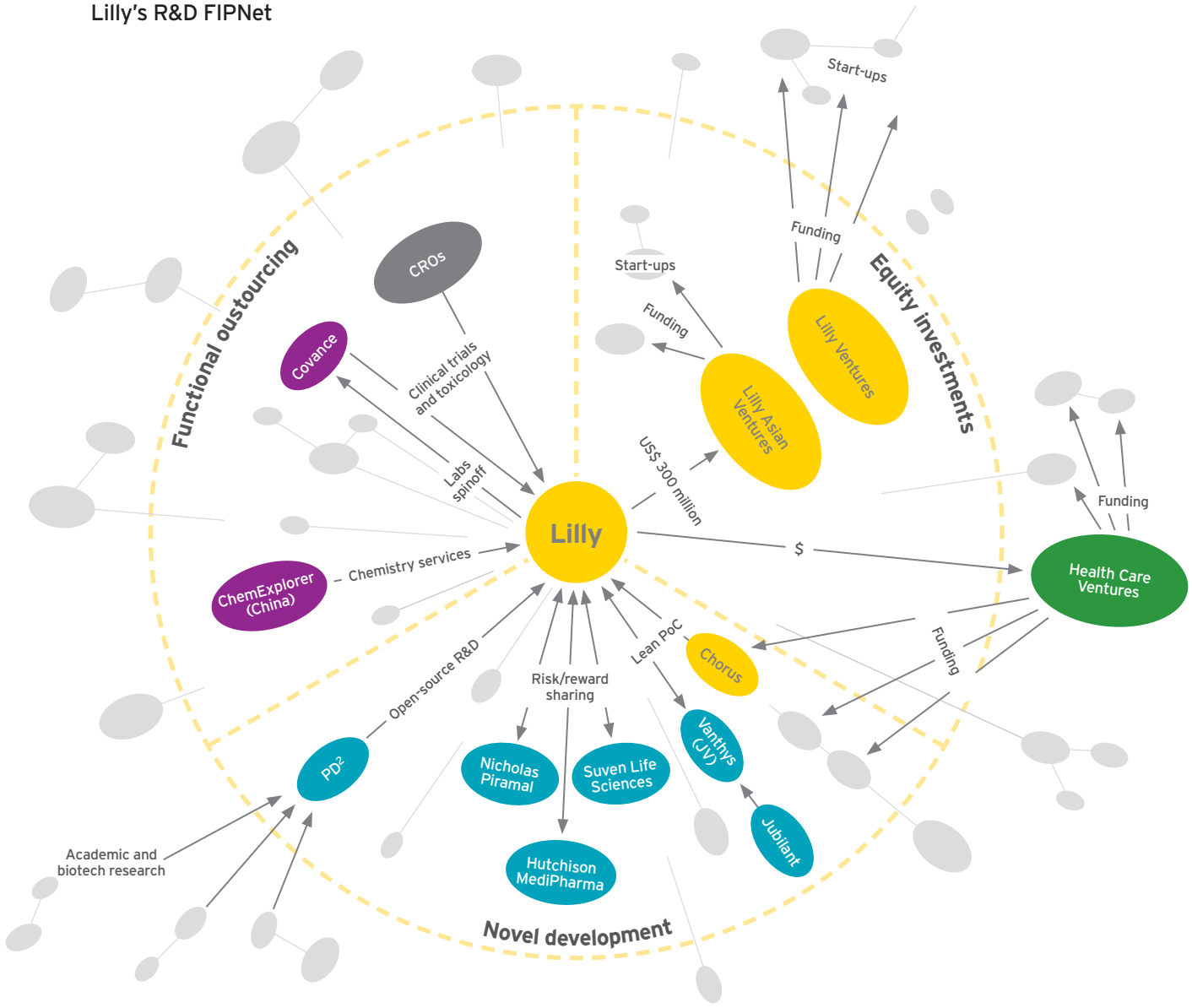
In 2008, we extended the Chorus model in India through a collaboration with Jubilant Organosys. Lilly will provide drug candidates to be advanced to proof of concept by a joint venture called Vanthys, and we will receive a right of first negotiation on non-Lilly assets developed by the JV — those sourced by Jubilant or other third parties.

We've also launched an "open source" R&D platform, our Phenotypic Drug Discovery Initiative. Through "PD^2" Lilly tests, free of charge, compounds submitted by outside researchers in four assays representing diseases of interest to us. In return, we retain first rights to negotiate a collaboration or licensing agreement with the submitters. If such an agreement does not result, the external researcher receives no-strings-attached ownership of the data report to use as they see fit in publications, grant proposals or further research. Since the launch of PD^2 in June 2009, 130 universities and biotechs in 21 countries have joined the program, and we're now evaluating thousands of molecules.

The third area of FIPNet includes **equity investments** and **partnerships**. Our Lilly Ventures and Lilly Asian Ventures — with a combined US$300 million in funds — are investing in emerging biotech, health care IT and medical technology companies in the US and around the world. These investments enable us to evaluate and advance emerging technology that may play a role in long-term opportunities for Lilly, and even to build companies such as HD Biosciences in Shanghai that can provide critical capabilities in our FIPNet.

We recently established a new venture capital fund with HealthCare Ventures, which will enable the acquisition of high-quality molecules from external sources and utilize Chorus and other alternative development engines to advance them to proof of concept, with

Lilly's R&D FIPNet



Source: Ernst & Young and Eli Lilly and Company

Lilly all the while retaining preferential access to acquire the molecules.

We've tapped other private investment funds to spread the risks of certain late-stage R&D projects, and we're working with partners to bridge the so-called valley of death. This is the phase in development where funding often dries up before a promising molecule can be translated into a potential medicine that would attract new investment. We're hopeful that a collaborative approach can give new life to molecules discovered at research institutions and biotech companies.

The success of our FIPNet strategy is inextricably tied to the success of our partners, and our network is only as strong as our partners. This point is especially critical today, when investment capital is drying up for many small biotechnology companies. Biotech firms and other potential partners have much to gain from joining our FIPNet – new business opportunities, new and enhanced capabilities and even new investment capital.

If FIPNet is to be a source of strength – and not a drain on time, attention and resources – we at Lilly must maintain a focus on the core capabilities and senior management skills necessary to manage a diverse and growing portfolio. Our success as the architect of this network demands that we understand the needs of our partners, that we share knowledge with them and that *we* make decisions as quickly as *they* can. And all partners – Lilly included – must demonstrate flexibility, open and honest communication, collaboration and a steadfast commitment to common goals.

The relationships we're building across our FIPNet are true "force multipliers," providing Lilly with more innovative molecules and helping us move them through early development faster and at less cost than in the past. We believe FIPNet is a critical tool for Lilly's innovation engine, enabling us to speed a new generation of important medicines to patients. ▶

New opportunities

Country profiles

Conversation on emerging markets

New opportunities

Kiran Mazumdar-Shaw
Biocon
CEO

Canwen Jiang, MD, PhD
Genzyme
Vice President and Head of Genzyme R&D Asia

Emerging markets have attracted increasing attention from Western companies in recent years, driven by the brisk growth and tremendous potential in these markets, as well as the rapidly evolving strengths of new generations of companies in these locations. As we surveyed the "new normal" for this year's *Beyond borders*, we wondered how changing market realities have affected these trends. Has the performance of companies in emerging markets been hurt by the global economic downturn? As biotech companies in the West adjust to the new normal and the need to find new sources of efficiency, what role are companies in emerging markets playing?

To get some perspectives on these questions, we sat down in early 2010 with a couple of industry leaders from two emerging-market giants — India and China. Canwen Jiang, Vice President and Head of R&D for Genzyme R&D Asia, has been with the Massachusetts-based company since 1994 and currently heads Genzyme's R&D operations and strategy in the Asia markets with a focus on China. Kiran Mazumdar-Shaw is the long-tenured CEO of Bangalore-based Biocon, a leading Indian biotech compan that provides services through its Syngene and Clinigene units while also developing novel biopharmaceuticals.

The picture these two leaders paint is encouraging. Not only have emerging markets survived the downturn, but many firms in these locations have even benefited from their ability to provide the very efficiencies that Western firms are seeking. As companies in the West look for new approaches to sustainability, they will increasingly need to look at emerging markets in new ways.

Ernst & Young: What impact did the global economic downturn have on the biotech industry in China and India? What's the situation today? Is a "new normal" emerging after the dust has settled?

Jiang: China's experience has been quite different from what happened in the West. On one hand, the Government has started providing very significant funding for life-sciences start-ups. Policy-makers view this as a strategic long-term investment in building a knowledge-based economy. As a result, China remains an attractive location for companies, including Western companies which are moving to China to take advantage of the infrastructure that's been built.

On the other hand, China is part of the global economy and an important player in the globalization of drug R&D. So as Western companies — particularly early-stage companies — have faced financial difficulties, they have had to cut back on their spending in China, for instance with Chinese CROs.

Mazumdar-Shaw: The global recession hasn't hurt the Indian biotech industry. The overall Indian economy has been largely insulated from the economic downturn, and the Indian biotech sector has actually benefited from what's happening in the rest of the world.

Biotech and pharma companies in the West are under strain, not just because of the financial crisis, but because of their R&D pipeline challenges and the need to control costs amid stagnating top-line growth. Since Western companies are finding it difficult to create significant growth in developed markets, they are increasingly looking at emerging markets. Other growth strategies being pursued by big pharma include portfolio diversification through products with lower regulatory timelines – generics, biogenerics, devices, diagnostics and vaccines. And emerging markets with lower cost profiles, such as India and China, are beneficiaries of this fallout since they provide unique solutions to many of these problems.

Ernst & Young: Could you discuss your activities and strategy in your respective markets? What growth opportunities do you see over the next five years and where do you see your company at that point?

Mazumdar-Shaw: Biocon started its business transformation about 10 years ago, from developing enzymes to developing biopharmaceuticals. We now have a very risk-balanced portfolio of products – a rare combination of small-molecule generic APIs, insulin-based biogenerics and biosimilar monoclonal antibodies, as well as novel drugs. Our biogeneric insulins offer a very large market opportunity due to the dramatic growth rate prevalent in diabetes. For biosimilars, we have partnered with US-based Mylan Pharmaceuticals. We anticipate building emerging markets first and then following this by expanding to developed markets a few years later.

Our services business is also strong. While the tremendous pressure on pharma companies to reduce R&D costs has boosted outsourcing, some CROs were badly affected by megamergers such as Pfizer/Wyeth and Merck/Schering-Plough. Many outsourcing agreements – some quite substantial – were frozen as companies worked out their new organizational models. We have been lucky that our largest customer, Bristol-Myers Squibb, has not been distracted by any large transactions. As Western companies continue to focus on reducing headcount and R&D costs, we anticipate more growth in our services business. Unlike most CROs, we have capabilities in both small molecules and biologics, and we can realistically expect 20%-plus growth in our services business.

> "As Western companies continue to focus on reducing headcount and R&D costs, we anticipate ... 20%-plus growth in our services business."

Jiang: The Chinese market is strategically very important for Genzyme. We already have several products on the market, some of which are doing very well. We are also building an R&D Center in Beijing which will focus on diseases important for China and other Asian countries. We have been providing some products on a charitable basis for some time and we are now working with the Government to achieve sustainable funding mechanisms for serving patients in these areas.

In the next five years, I think we will have a significant number of products registered and marketed in China. Our goal is to be the market leader in the Chinese biotech space.

Ernst & Young: What are the biggest challenges and risks in India and China today? What advice would you give Western companies looking to set up local operations and/or partner with local firms?

Jiang: The biggest challenge for Western companies is to really understand the local market, including the local culture, available resources, infrastructure and Government policies. The Chinese market is not fully mature – R&D infrastructure is being built, and resource-allocation mechanisms are significantly different from what we are familiar with in the West.

"The biggest challenge for Western companies is to really understand the local market, including the local culture, available resources, infrastructure and Government policies."

So my advice to companies moving into China is threefold. First, really do your homework and understand the local market. Second, tailor your business model to your specific needs and the nature of the local market. Third, partner with local entities – companies, governments, and academic and medical institutions – to navigate the market.

Mazumdar-Shaw: I agree completely that partnering with local companies has its merits. For example, as national health systems struggle with containing costs, they will inevitably need to rely on tender-based procurement from the private sector. But to win these sizeable contracts, it is important to partner with a regional company that knows the landscape and can bid much more aggressively than a big or foreign firm could do on its own.

One other area that is often underestimated is the significant investment – both in time and money – necessary to establish your brand in a new market. Partnering with a regional company and leveraging its distribution network will allow much faster market entry and bigger gains in market share.

But probably the biggest risk and challenge to any new market, particularly markets as complex as India and China, is awareness of the regulatory regime. This may be the biggest benefit in partnering with a local company that is more adept and up-to-date with the increasingly changing regulatory landscape in these markets.

Ernst & Young: In the current climate, many Western companies need new models for raising capital creatively, tapping alternative sources of revenue and operating more efficiently. Given that Asian firms have often developed models different from the typical Western biotech model, what lessons, if any, could Western firms learn from their Asian counterparts?

Mazumdar-Shaw: Western biotechs tend to be dependent on a very high-risk, all-or-nothing business model funded by VC firms looking for timely returns on investment. This puts a lot of pressure on companies to find a path to an exit, because VCs have a limited investment horizon. Of course, if a drug candidate fails, the company is often finished unless it can find more funding to go on to something else.

We can't afford that sort of operating model in India, because risk capital is largely unavailable for Indian biotech companies. Our businesses are mostly debt-funded. A bank isn't looking for a VC-style "exit" – it simply wants you to pay back your loan by managing risk well and building a sustainable, profitable business. Companies like Biocon are self-funded – we use revenues from our product and services to fund our R&D pipeline. So Indian companies have to carefully manage risk in making R&D choices and determining their business mix. For Western biotechs, the lesson may be in how you approach your business model – are you building an investment opportunity or building a sustainable business?

Jiang: The "standard" biotech business model has served Western patients and economies wonderfully for decades. Now, we need to serve the needs of patients in emerging markets. And to do that, we need new thinking and new business models. Of course, Western companies should preserve good corporate principles and bring them to emerging markets, including quality, ethics and legal protections. But the biggest mistake they could make is coming in with preconceived notions and doing everything "as usual."

In the area of talent, for instance, one mistake multinationals can make is to not fully appreciate and utilize the potential of local talent. There is always an adjustment period during which

"The 'standard' biotech business model has served Western patients and economies wonderfully for decades. Now, we need to serve the needs of patients in emerging markets. And to do that, we need new thinking and new business models."

local colleges try to understand Western corporate culture, and companies need some patience while that happens.

Ernst & Young: What's your outlook for the Chinese/Indian biopharmaceutical industry? In which segments do you see the most growth occurring? What regulatory or other changes are required for the sector to fully realize its potential?

Jiang: It's hard to make predictions about any specific segment, but I think it's clear that biologics are poised for growth in China, as more and more people look for products that are highly efficacious and specific. Vaccines will play a very important role in addressing public health issues. Of course, generics and branded generics have tremendous growth potential as the Government expands health care access in rural areas — but I expect the truly explosive growth over the next 5 to 10 years to be in high-end, innovative products.

Mazumdar-Shaw: I would like to see better harmonization of the Indian regulatory system with the US FDA. This would allow both countries to leverage each other's strengths to create "affordable innovation." The US has a wealth of intellectual property sitting on shelves, and India can play a huge role in developing and commercializing these assets in affordable ways. Innovation in the West has simply become unaffordable, so much so that when a new drug finally comes out, it has to be priced at a level many patients can't afford. But I'm starting to see a shift in thinking as big pharma companies become more comfortable working with countries such as India for more affordable R&D services. Western pharma and biotech companies are now coming to us and saying, "we've got some assets — can we co-develop them with you?" This never used to happen in the past. But as economic pressures continue, this is the time for companies to really benefit from going beyond borders. ▶

"Western pharma and biotech companies are now coming to us and saying, 'we've got some assets — can we co-develop them with you?' This never used to happen in the past."

China year in review

Accelerating reforms

It is evident that China will be an increasingly important market for biotechnology and pharmaceutical products and companies in the years to come. Indeed, it is now considered essential for companies with commercial operations or aspirations to formulate a strategy for the Chinese market — a market currently dominated by generics (including generic versions of Western biologic drugs) and traditional Chinese medicines (TCMs). Meanwhile, the Chinese Government is encouraging the development of a domestic innovative biotechnology sector through a combination of direct investment, intellectual property reforms and commercial incentives. Yet for all the promise, the sheer volume of change — driven both by market dynamics and Government reforms — is daunting, creating uncertainties for investors in China's biotech sector.

Growth and consolidation

China's pharmaceutical market continues to post impressive year-over-year growth driven by macro trends — an aging population, Government programs to significantly broaden access to medicines, increasing personal wealth and the increasing incidence of "middle class diseases," such as diabetes and hypertension. A recent IMS Health report pegged the market's annual growth rate at 27% from 2006 to 2009 and projected that China would surpass Germany and France to become the third-largest drug market in the world by 2011 (behind only the US and Japan).

At present, the industry is highly fragmented, with several thousand domestic manufacturers and distributors competing alongside most of the major multinational companies from the US, Europe and Japan. To boost efficiency and quality, the Government is encouraging consolidation of the domestic industry, partially through changes to the drug distribution system and price reforms. It is aiming to reshape the industry with fewer financially strong entities that have the scale necessary to undertake national distribution and investments in innovative R&D and, eventually, compete globally through exports.

Beyond the market opportunity, China remains a highly attractive outsourcing destination in terms of cost efficiency and, increasingly, patient availability for clinical trials, expertise and infrastructure.

Essential reform

In March 2009, China adopted a massive reform of the health care system, committing RMB 850 billion (US$124 billion) over the next three years to increase health insurance for the non-employed urban and rural populations. While health care reform was driven by the realization that a healthy population is necessary to sustain economic growth, the 2009 policies were accelerated by the global recession. Chinese leaders concluded that the country needed to decrease its dependence on exports while maintaining employment levels through encouraging domestic consumption. The Chinese population has historically had a very high savings rate, in part to save for unexpected and uncovered medical expenditures; thus, providing greater health coverage will presumably free up capacity for non-health related spending. The increased coverage will lead to higher pharmaceutical sales, but distribution to second- and third-tier cities and rural populations will remain a challenge for many manufacturers.

Beyond health insurance coverage, the Government is also addressing the drug distribution process itself as part of the reform efforts. A significant majority of drug sales are now made through state-owned hospitals. Hospitals depend on the margin from these sales (generally 15%) to fund their operations and are therefore motivated to prescribe higher-priced medicines to maximize the margin earned. This drives up overall system costs and creates an environment that encourages improper sales practices.

Finally, in August 2009, China updated its Essential Drugs List (EDL), which includes 307 medicines that will be given priority from a usage and reimbursement standpoint. Approximately two-thirds of the EDL is composed of products discovered and developed outside China (most of which are available in generic form in China already) and one-third is composed of TCMs. The Government will set the prices for drugs on the EDL, which will put a premium on cost-effective manufacturing and distribution and generally benefit larger players. Innovative and patented drugs sold by multinational companies will continue to be funded largely by patients.

Despite their higher cost, brand-name drugs that no longer have patent protection are often favored by populations in more affluent urban settings as they are perceived to be of higher quality than generic competitors.

After the product-quality scares of recent years, the Government reforms are also focused on enhancing overall drug safety and manufacturing quality, including enhancing Good Manufacturing Practice requirements (for more information, see *A closer look* on this page).

The innovation future

The Chinese Government identified biomedicine as one of the strategic focus areas under its 11th Five-Year Plan (2006–2010). Among the main aims of the plan are securing the economic structure, urbanizing the population, conserving energy and national resources, encouraging sound environmental protection and improving education. In addition, the plan seeks to increase access to employment and medical care and to improve pensions for the elderly. The 12th Five-Year Plan, now under development, is expected to focus on, among other things, fostering an innovation economy with biotechnology as one of the targeted industries.

Biotech innovation incentives

In May 2009, the State Council, China's cabinet, announced a program to spend RMB 62.8 billion (US$9.2 billion) by the end of 2010 in support of technologies in several industries, including biotechnology. The program also called for preferential Government purchasing of locally developed products – a concern for foreign manufacturers – and specialized investment funds and agencies to channel funding into the industry, as well as certain preferential tax deductions for research and development expenses. In

A closer look

Providing incentives to encourage continuous quality improvement

Cherrie Che
Ernst & Young Advisory Services Ltd

Good Manufacturing Practices (GMP or cGMP in the US) are the "floor level" requirement for life sciences enterprises to operate. Leading companies have made additional efforts, mostly on a voluntary basis, to pursue more robust quality management measures.

In China, the implementation of GMP standards has been a step-by-step process. Starting with the manufacturers of blood products, which was the first group required to complete GMP certification in 1998, all drug preparation manufacturers had to be in compliance by 2004. At present, the State Food and Drug Administration (SFDA) is driving to upgrade the GMP requirements, with new rules due to be promulgated in 2010.

Upgrading the GMP standards demonstrates government and industry focus on continuous improvement in the quality of life sciences products. A series of recent projects undertaken by Ernst & Young and sponsored by the China Association of Enterprises with Foreign Investments' R&D-based Pharmaceutical Association Committee (RDPAC) and the Pharmaceutical Research and Manufacturers of America (PhRMA) found potential quality gaps among products from GMP-certified pharmaceutical companies as a result of the different practices in quality management. This research project highlighted that product testing alone is not sufficient to safeguard the quality of pharmaceutical products. It is critical to establish and maintain a robust quality system to ensure consistent production of high-quality products. Another important finding from the project was that significant investment is required to establish and maintain a quality system. To encourage the industry to focus continuously on improving quality management, the project report concluded that the Government should consider putting incentives in place, including rewarding a price premium to products supplied by a company with a robust quality system.

addition, the Government committed to enhancing the protection of intellectual property rights and steps to ensure the safe use of biological technologies and products. Priority sectors include biopharmaceuticals, agricultural biotech, bioenergy, biomanufacturing and bioenvironmental protection.

Accelerated process for new drug approvals

In 2009, the State Food and Drug Administration (SFDA) issued its special procedure to accelerate the approval of four categories of drugs: 1) active pharmaceutical ingredients (APIs) new to the Chinese market; 2) drugs, APIs or biologic products that have not been approved worldwide; 3) new treatment for AIDS, cancer and other rare diseases with significant efficacy over current treatments; and 4) new drugs targeting unmet medical needs. Under the fast-track procedure, the SFDA's Center for Drug Evaluation (CDE) has five days to decide whether to accept the application if the drug is eligible under the first and second categories. For drugs under the third and forth categories, the CDE has 20 days to respond to the application. The fast-track procedure shortens the approval period for investigational new drugs (INDs) from 90 days to 80 days and the New Drug Application (NDA) timeline from 150 days to 120 days.

Pre-IND meetings have also been introduced to the fast-track approval mechanism. Similar to the US FDA's pre-IND meetings, the mechanism encourages discussion of specific drug development issues in advance to expedite approval and understand the SFDA's position. This procedure is particularly effective when the sponsor's questions are not fully addressed by guidance or other information provided by the agency.

These changes in the new drug approval process seek to make China a preferred country for simultaneous global drug development programs and enable earlier product launches to benefit patients in China.

Intellectual property reform

The "third amendment" to China's patent law came into effect in October 2009 and further strengthens intellectual property protection for innovative discoveries by bringing the rules closer to international standards. Major changes include higher damages for patent infringement and the adoption of an "absolute novelty" standard, meaning that the invention must be novel globally, not just in China, to be patentable. This will allow challenges to the issuance of Chinese patents where prior art is known to exist outside of China.

The rules also seek to encourage foreign patent filings on Chinese inventions by removing the requirement to file first in China. However, prior to filing a patent in a foreign jurisdiction, inventors must make a confidential filing with the patent office for a national security clearance. Similar to US law, the new rules also permit generic drug makers to utilize a patented medicine for the purposes of regulatory and administrative filings, which benefits generic drug makers preparing to market a product rapidly after patent expiration.

Finally, of particular relevance to the biotech industry is a new requirement that inventions that depend on "genetic resources" disclose the direct source of such resources or disclose why the applicant is unable to do so. While the term "genetic resources" is not precisely defined, it is expected to be interpreted broadly. In addition, the genetic material must have been obtained in accordance with applicable laws. Although the protection of genetic diversity has been discussed by and among many emerging countries, China is the first to require

disclosure of the source of such material in its patent regulations.

Science parks

Science parks have been established with the support of the Government to foster strong industry and academic collaboration and achieve early translation of research into commercial applications. Shanghai Zhangjiang Hi-Tech Park, which was among the earliest science parks in China, has become the base for nearly 100 companies. The park includes multinational pharma companies such as Pfizer and Roche, contract research organizations (CROs) like WuXi AppTec and start-up research-based companies, such as Hutchison MediPharma, MicroPort and Genon Bio-engineering.

Beijing Zhongguancun Life Science Park is located adjacent to such world-class universities as Peking University and Tsinghau University. The easy access to novel research institutions has led many world-leading life sciences companies to establish their R&D centers in the park. In September 2009, Genzyme was the first large US biotech player to establish R&D capabilities in China through a US$90 million facility that is anticipated to be completed in 2010. (For more on Genzyme's plans in China, see the interview with Canwen Jiang in the "Conversation on emerging markets.")

China Medical City, a pharmaceuticals-focused park located in the eastern province of Jiangsu, was established as recently as 2008 but has quickly achieved a newcomer's advantage. In 2009, GlaxoSmithKline chose the park for a vaccine R&D and manufacturing joint venture.

Deals

M&A and alliance activity remained modest in China in 2009 compared with more mature biotech markets. On the M&A front, most acquisitions were between domestic Chinese companies seeking to expand product portfolios in the generic and TCM space and capture distribution efficiencies. There was limited transaction activity in or among innovative biotechnology companies, which is not surprising given the nascent stage of development of this segment of the industry.

In January, Genesis Pharmaceuticals acquired Hongrui Pharmaceuticals for approximately US$12 million. In the transaction, Genesis gained access to 22 TCM products marketed by Hongrui. In October 2009, China Medicine Corporation acquired LifeTech Pharmaceuticals, another TCM company with a broad portfolio. The single largest acquisition of a TCM player was actually a management buyout of Sihuan Pharmaceuticals, which had been listed on the Singapore stock exchange, by Morgan Stanley Private Equity in a transaction valued at US$318 million.

The most significant inbound transaction of the year, which has not yet been finalized pending approval from the Chinese authorities, was Novartis' proposed acquisition of an 85% stake in Zhejiang Tianyuan Bio-Pharmaceutical Co., a maker of vaccines for influenza and hemorrhagic fever, for US$125 million. In September, US-based PerkinElmer acquired SYM-BIO Lifescience, a provider of diagnostic instruments and reagents for US$64 million.

Simcere Pharmaceutical Group followed up its 2008 acquisition of a majority stake in Wuhu Zhong Ren Pharmaceutical Co. with two minority investments in 2009. Simcere became the largest shareholder in Jiangsu Yanshen Biological, a vaccine manufacturer, by acquiring a 37.5% interest in the company for US$29 million. Simcere also acquired a 35% stake in Shanghai Celgen Bio-Pharmaceutical Co., a producer of generic therapeutic antibodies. Interestingly, the transaction can be unwound by Simcere if the SFDA does not approve a specified Shanghai Celgen biogeneric drug within 24 months.

Financing

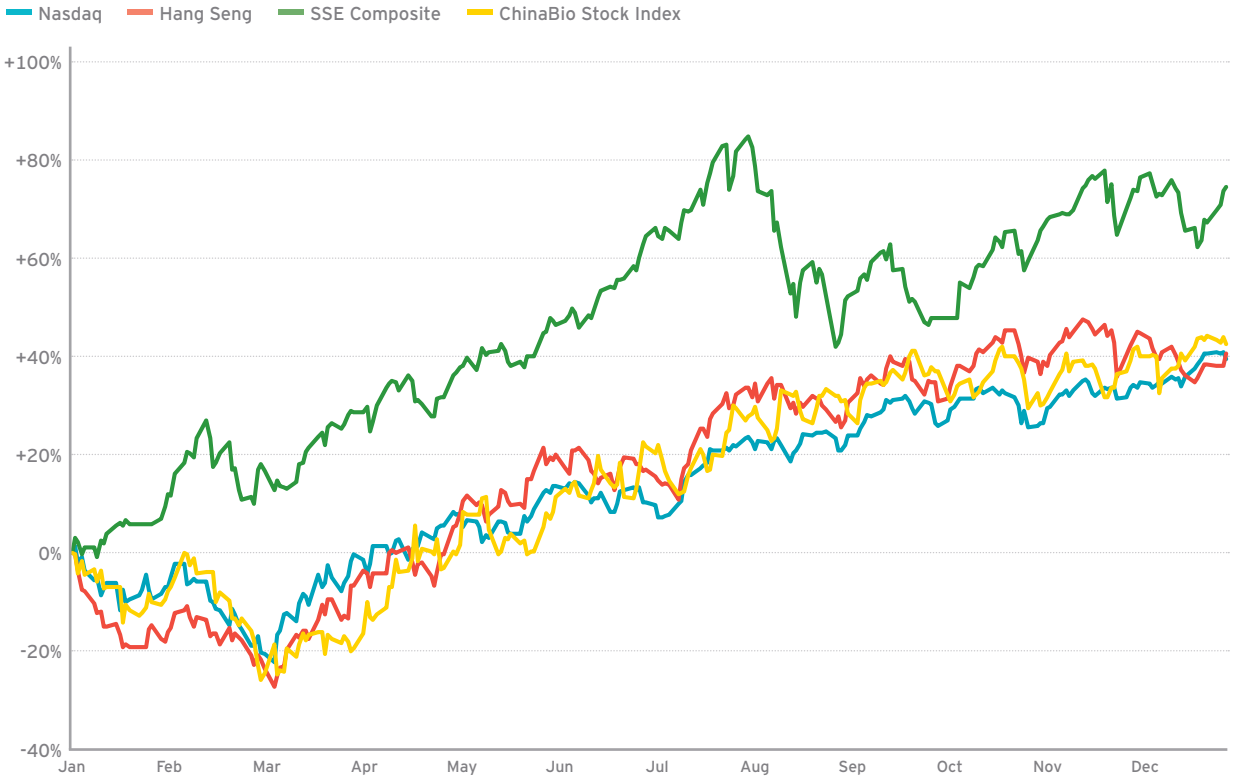
In 2009, the ChinaBio Stock Index, which comprises 18 biopharmaceutical companies, rose 42%, largely reversing its 57% decline of the prior year. As in 2008, the Index largely tracked other stock market indices in 2009: Hong Kong's benchmark Hang Seng Index was up 40%, the NASDAQ was up 40% and Shanghai's SSE Composite Index was up 74%.

Venture capital

Health care venture capital investment remains relatively modest in China. Statistics from ChinaVenture indicate that total venture capital investment in China declined by 25% to US$3.8 billion, reversing a multiyear growth trend. ChinaVenture counts 47 transactions in the health care sector aggregating US$416 million, or 11% of the total, which represented an increase over 2008 levels.

While venture investors in China see the tremendous market potential in the country's health care market, the investments to date have focused for the most part on relatively lower risk areas, such as clinical research, manufacturing and distribution companies. These companies tend to generate cash flows from operations and therefore have

In 2009, overseas-listed Chinese biotech companies rose along with broader market indices



Source: Ernst & Young, CapitalIQ and ChinaBio Today

lower investment risk, especially when one considers the changing regulatory, reimbursement and intellectual property situation that must be added to the risk of novel drug discovery.

Innovation-focused companies are likely to garner a larger share of venture investments over time as regulatory uncertainty diminishes and Government support for research finds its way into the market. Chinese companies have a variety of potential innovation models to pursue, including: "end-to-end" discovery and development, leveraging China's cost advantages with the possibility of out-licensing ex-China rights; in-licensing technologies from US or European companies for development in China; and developing and clinically testing TCMs to bring to market outside China.

Among the notable venture investments in mainland China in 2009 was the US$15 million raised by CRO Jinsite Science and Technology in a round led by US venture firm Kleiner Perkins Caufield & Byers. TCM maker and distributor Sinocom Pharmaceutical also raised US$15 million. Novast Pharmaceuticals, which develops, manufactures and markets generics, raised US$25 million in a Series C round that included participation by NEA, Lilly Ventures and Qiming Ventures, among others. NEA also joined BioVeda China Fund to invest an undisclosed amount in the re-start of Nexchem, an API manufacturer.

It is also worth noting that not all of the venture activity was centered in mainland China. Taipei-based TaiGen Biotechnology Co., Ltd., which is focused on developing drugs to treat infectious diseases, cancer and diabetes-related complications, raised US$37 million in a Series C round from investors that included MPM Capital, National Development Fund, YFY Group, Taiwan Sugar Corporation, Yao-Hwa Glass Management Commission and Taiwan Global BioFund. And Taiwan Liposome Company raised US$4.5 million in a round led by YFY Biotech Management, along with Burrill & Co. and Boston Life Science Venture Corp.

IPOs

Overall, 2009 was a strong year for IPOs in both Hong Kong and mainland China. Aggregate funds raised through IPOs in Hong Kong exceeded US$31 billion and in Shanghai exceeded US$27 billion. The Shanghai Stock Exchange ranked third biggest in terms of total IPO funds raised during the year, trailing only the Hong Kong and New York Stock Exchanges.

There were no health care-related IPOs until the second half of 2009, after the lifting of a Government ban on new issues. From July to December, however, five generic or TCM pharmaceutical companies listed on the Shenzhen Small and Medium Enterprise Board. Guilan Sanjin Pharmaceutical Co., a TCM company, was the first IPO from any industry and attracted significant investor interest, raising RMB 911 million (US$133 million). In October, the Shenzhen Exchange launched its NASDAQ-style board, ChiNext, and five pharmaceutical companies completed IPOs on the board through year-end, raising total funds of RMB 2.8 billion (US$410 million). The largest health care IPO of the year was that of state-owned drug distribution company Sinopharm Group, which raised more than US$1 billion on the Hong Kong exchange.

The only Chinese biotech company to complete an IPO on NASDAQ in 2009 was China Nuokang Bio-Pharmaceutical, which is focused on the research, development, manufacture, marketing and sales of hematological and cardiovascular products. The company, whose primary product is an anti-coagulant derived from the venom of a pit viper, raised US$45 million.

To date most, if not all, Chinese IPOs have had revenue and profits from either product sales or services. As the industry moves toward a greater focus on innovation, continued access to capital from public investors will be critical. It is unclear whether investors in the domestic Chinese markets will have the same risk appetite for early-stage companies as investors in the US; thus, IPOs on NASDAQ or other US markets may prove to be more common.

Outlook

In addition to a large and ever-expanding market for existing pharmaceutical products, the medium- to long-term trends for the emergence of an innovation-based biotechnology industry in China appear positive. The Government's financial support, strong academic research, emerging science parks and growing sources of venture capital are all important ingredients. However, Government policies will have to provide the right incentives in terms of financial return commensurate with new product development risk and will have to further strengthen intellectual property protections for innovators. In addition, Chinese innovators will need a global outlook to attract corporate partners who can provide expertise, market access and capital. But the backdrop of dramatic health care and regulatory reform and industry consolidation in the domestic pharmaceutical market make the actual pace of change hard to predict. ▶

Chinese biopharmaceutical IPOs on domestic exchanges, 2009

Company	Month	Exchange	Amount raised (US$m)
Guilin Sanjin Pharmaceutical	July	Shanghai (SME)	133.2
Tibet Cheezheng Tibetan Medicine	August	Shanghai (SME)	70.8
Sinopharm Group	September	Hong Kong (HK Main)	1,295.40
Shenzhen Salubris Pharmaceuticals	September	Shanghai (SME)	174.8
Tianjin Chase Sun Pharmaceutical	October	Shenzhen (ChiNext)	110.4
Beijing Beilu Pharmaceutical	October	Shenzhen (ChiNext)	44.5
Anhui Anke Biotechnology Group	October	Shenzhen (ChiNext)	52.2
Chongqing Lummy Pharmaceutical	October	Shenzhen (ChiNext)	55.4
Zhejiang Xianju Pharmaceutical	December	Shanghai (SME)	102.4
Shanghai Kaibao Pharmaceutical	December	Shenzhen (ChiNext)	152.3
Guangdong Zhongsheng Pharmaceutical	December	Shanghai (SME)	160.9

Source: Ernst & Young and Bloomberg
Currency conversion taken from the first day of the IPO month.

India year in review

Preparing for the opportunities ahead

India's biotech industry has blossomed in recent years, as domestic companies have grown aggressively in a liberalized intellectual property (IP) regime and as companies everywhere have sought to seize opportunities from the country's large, skilled workforce, lower manufacturing and research costs and the growing demand for health care. Unlike biotech sectors in many parts of the world, the Indian biotech industry, which has been less reliant on capital from investors, was not hurt by the global recession — indeed, many domestic companies were positioned to benefit from the increased focus on cost-cutting in the West. The year saw significant developments on several fronts, as well as some setbacks.

Regulatory reform: the quest continues

India's move toward a standardized approval system continues. A bill to establish a centralized National Biotechnology Regulatory Authority (NBRA) to approve the majority of biotech products — initially drafted in July 2008 (see last year's *Beyond borders* for more details) — is currently open for comments from industry and other stakeholders. The regulatory reform drive got an unexpected push from an unlikely source, the Bt brinjal controversy (discussed later in this article), and some industry watchers anticipate that the bill could be introduced in Parliament during the first half of 2010. While it faces strong opposition from the lobby against genetically modified (GM) crops, the industry views the establishment of the NBRA as critical for boosting its global competitiveness.

Even as India moves toward a centralized regulatory authority, segment-specific issues will need to be addressed with specific regulations. In June 2009, the central Government proposed a national policy on vaccines to create a separate vaccine regulatory authority. The proposal — currently being drafted by the Ministry of Health and the Indian Council of Medical Research (ICMR) — aims to streamline production and boost the viability and affordability of essential vaccines, particularly for the national immunization program. The policy is also likely to give preference to public sector undertakings (PSUs) for manufacturing vaccines for the national immunization program.

To streamline the growing clinical research industry in the country, the Drug Controller General of India (DCGI) drafted a proposal to make mandatory the registration of all clinical trials as well as Clinical Research Organizations (CROs). The proposal includes guidelines on proper documentation and standard operating procedures for various trial-related tasks carried out by CROs.

New legislation is also being considered to boost incentives for commercializing intellectual property generated by publicly funded research projects. The lack of such incentives has historically resulted in the underutilization of IP from such projects, especially in academic institutions.

Agricultural biotech: the Bt brinjal issue

With almost 60% of India's population directly or indirectly engaged in agriculture, major agricultural policy changes can be controversial. This was manifested in the agricultural biotechnology segment when the government put the commercial cultivation of genetically engineered eggplant, Bt brinjal, on hold in February 2010 after facing strong opposition from states and various environmental groups. This decision was taken despite the fact that India's agriculture ministry and the Genetic Engineering Approval Committee (GEAC, the main regulatory body responsible for genetically engineered organisms) certified the safety of this eggplant variety for commercial release. Had Bt brinjal received commercial cultivation approvals, it would have been the first GM food crop to enter the Indian market and the world's first-ever GM vegetable to be grown on a large scale.

India has been conducting field trials on GM versions of crops, including rice, mustard, cauliflower and peas, for nearly a decade but has not approved any GM crop except cotton. The failure of Bt brinjal to reach the market could create hurdles for the clearance of the approximately 40 GM food crop applications currently pending. However, the controversy has boosted arguments for a single-window clearance mechanism for all aspects of biotechnology regulation.

Stem cell research

Indian companies have been active in the area of stem cell research. In March 2009, Stempeutics Research received an approval from the DCGI to conduct human clinical trials for drugs using stem cells. India is now the second country, after the US, to allow human clinical trials for drugs using dormant cells in the body with natural regeneration capabilities.

Singapore-based CordLife established cord-cell banks in India in November 2009. Fortis

Healthcare, a leading private health services provider, tied up with Beike Biotech in June 2009 to conduct clinical trials for a stem cell therapy for diabetic foot ulcers. Meanwhile, another major health care player, Apollo Hospitals, announced the establishment of a public stem cell bank and a stem cell research unit in collaboration with Cadila Pharmaceuticals and StemCyte India Therapeutics.

To drive growth in this emerging field, ICMR is drafting guidelines for stem cell research through the Biomedical Research on Human Subjects (Promotion and Regulation) bill. The bill — likely to be introduced in Parliament in 2010 — would allow stem cell research and therapeutic cloning while restricting human reproductive cloning until its safety and benefits are proven. A defined regulatory pathway and its effective implementation would further boost stem cell research.

Infrastructure development

India's central government and various state governments in collaboration with private players continued to announce new infrastructure investments, especially in the form of new biotechnology parks and clusters. A new biotechnology park being set up by infrastructure player Ansals API at an investment of around US$220 million is likely to be commissioned in Lucknow by the end of 2010.

The Government is developing three major biotech clusters, at Mohali in Punjab, Faridabad in Haryana and Bangalore in Karnataka. The Department of Biotechnology has approved the establishment of a marine biotechnology research institute in Kerala at an investment of around US$45 million. In South India, the Andhra Pradesh government announced plans to set up four biotech special economic zones in the state, while the state of Karnataka unveiled its Millennium Biotech Policy II, including plans to build five biotech parks with the support of advanced research institutes, simplify approval processes for infrastructure investments and offer tax concessions to companies setting up base in the state. The northern state of Himachal Pradesh is setting up a biotechnology park using a public-private partnership. Other state governments such as Goa and Kerala also announced infrastructure development policies to establish biotechnology hubs in their states.

Financing

As in many emerging markets, research-based biotechnology companies in India have often had limited access to venture capital. As in much of the world, this situation was exacerbated by the global recession. Investments by venture capital and private equity firms fell to only US$22.6 million in three deals, sharply down from US$120 million garnered in nine such deals during 2008. Meanwhile, Avasthagen announced plans to float an IPO during 2010 through which it aims to raise around INR6–7 billion (US$13–15 million).

Inward investments

Growing domestic demand and cost advantages have led many global biotech and pharma players to establish marketing, manufacturing and R&D operations in India. In February 2010, US biotech major Biogen Idec announced plans to launch its entire drug portfolio, including Avonex, Tysabri and Fampridine, in India. Initially, the company was selling its blockbuster multiple sclerosis drug through a licensing agreement with Piramal Healthcare. In May 2009, Switzerland-based Lonza announced plans to set up a US$150 million R&D and manufacturing plant in Andhra Pradesh that will serve as a manufacturing base for the company's regional operations. Netherlands-based QIAGEN announced the establishment of a sales and distribution office in India. The company is also considering establishing production and R&D facilities.

Deals

The Indian biopharmaceutical deal space has been very active in recent years, reflecting the huge changes under way in the Indian and global markets. In 2009, the trend continued. The year saw the largest-ever acquisition in the Indian biotechnology space when French pharma major sanofi-aventis bought a leading Indian vaccine manufacturer, Shantha Biotechnics, for around US$660 million. Like many big pharma companies, sanofi-aventis is looking to increase its presence in emerging markets, and this acquisition gives it low-cost vaccine manufacturing capabilities as well as a pipeline of vaccines specifically targeted at developing markets. Merck KGaA acquired a small proteomic and genomic research company Bangalore Genei, for about US$8.8 million to boost its biosciences research capabilities in India.

Against a backdrop of low valuations, a number of Indian firms went shopping, too. India's largest pharmaceutical company, Daiichi-Ranbaxy, acquired product rights, IP and manufacturing facilities of Indian vaccine manufacturer Biovel Life Sciences for an undisclosed amount. Advanta India

acquired US-based hybrid sorghum seed producer Crosbyton Seed Company to strengthen its position in the US sorghum market.

In January 2010, Transgene Biotek entered into a licensing and technology transfer agreement with Dr. Reddy's Laboratories for manufacturing obesity-management drug Orlistat. Also in January, Saamya Biotech (India) Ltd. entered into a joint venture with Malaysian firm Perak Bio Corporation to set up a biopharmaceutical manufacturing unit in Malaysia.

An increasing number of global biotechnology companies are eyeing India as an important destination for executing their cost-cutting measures in response to restrictive capital markets and the need to increase efficiency. There has been a significant spurt in deals involving outsourcing, technology transfer and entry of foreign players to tap a burgeoning Indian biotechnology market. Bristol-Myers Squibb and Biocon's subsidiary Syngene announced the opening of their integrated drug discovery and development center at Biocon Park in March 2009. This 200,000 square-foot facility will house around 360 researchers and will span the drug discovery and development process from lead optimization up to Phase I and Phase II clinical studies. India's leading contract research and manufacturing service (CRAMS) player, Jubilant Organosys, entered a contract research agreement with US-based Endo Pharmaceuticals to develop preclinical candidates for oncology. In September 2009, Biocon entered an agreement with US-based Amylin Pharmaceuticals to develop diabetes products. The company also entered a partnership with global generic drug maker Mylan to manufacture and commercialize several generic biotech drugs globally. Meanwhile, several European biotechnology companies, such as Germany-based Biobase and UK-based Oxygen Healthcare, Crystec Pharma and Lena Nanoceutics, have announced plans to outsource their manufacturing through collaborations with Indian companies.

Biosimilars: the next big opportunity

Indian biopharmaceutical players have developed strong capabilities in the high-potential biosimilar space and have presence in almost all the biologics coming off patent. Companies such as Reliance Life Sciences, Biocon, Wockhardt, Shantha Biotech, Panacea Biotech and Intas Pharmaceuticals have been developing strong capabilities in this area. Biocon expects to bring its oral insulin to the US market by 2011 and has other biologics such as G-CSF and various monoclonal antibodies in its pipeline. Biocon is also expanding the application of its head and neck cancer monoclonal antibody, BIOMAb EGFR, and has launched cervical cancer clinical trials for this drug. Reliance Life Sciences recently launched its fourth biosimilar product, TPA Reteplase, in the domestic market and plans to launch three more products in 2010. The company also has approximately nine biopharmaceutical products in preclinical and clinical development. Cipla formed a joint venture called Biomab with a Chinese company for manufacturing of biosimilars. Dr. Reddy's, which has filgrastim (G-CSF) and rituximab in the market, claims to have a pipeline of eight generic biopharmaceuticals in various stages of development, including two in clinical development.

Although Indian companies seem well-positioned, they will likely face strong competition from large cash-rich generics firms such as Teva Pharmaceuticals, Mylan and Sandoz. Moreover, taking biosimilar drugs into developed markets is likely to involve strong regulatory challenges due to a potential requirement for submitting non-inferiority clinical trial data — which could require large expenditures. In addition, strong marketing clout will be required to effectively compete with large numbers of biosimilar brands. As such, it is likely that Indian companies will partner with larger players to navigate these challenges.

Outlook: the opportunities ahead

In recent years, the Indian biotech sector has been gradually transforming from fee-for-service provider to a strategic partner for the global biotechnology industry — a trend that continues with some significant recent deals between Western and Indian companies. As Western companies recover from the financial crisis and focus on opportunities in newer geographies and cost optimization, we could see more acquisitions of Indian biotechnology companies, particularly those in niche segments or having specialized innovative and/or manufacturing capabilities.

Still, challenges remain. The industry urgently needs a streamlined regulatory structure to continue to attract investments from foreign companies. To move up the value chain, Indian companies will increasingly need to develop novel drugs — a challenge because of the lack of sufficient venture capital.

The Indian biotechnology industry has come a long way and continues to grow even amid the global downturn as Western companies seek opportunities to lower costs and boost R&D efficiency. But to seize the next wave of opportunities — from the evolving biosimilars space to establishing a presence in developing novel drugs — Indian companies, investors and policy-makers will need to focus on addressing some of the critical challenges identified above. ▶

Japan year in review

Rekindling investment

Despite its status as the second-largest economy and pharmaceutical market in the world, Japan has a biotech industry that is relatively underdeveloped compared to other advanced economies. While there are different schools of thought on when to date the birth of the Japanese biotech industry, the 2002 IPOs of Trans Genic and AnGes are generally considered the first Japanese biotech IPOs. Since then, there have been only 25 additional Japanese biotechs that have gone public, the majority (16) listing on the Tokyo Stock Exchange (TSE) Mothers market, with the remaining 11 listing on other Japanese markets — Nagoya Stock Exchange (NSE) Centrex, Osaka Securities Exchange (OSE) Hercules and Jasdaq NEO. From 2002 to 2004, high expectations for the biotech industry fueled a run-up in the Nikkei BP Bio Index. However, investors — who did not always have a full appreciation of the long time frame to bring a drug from early research to market — soon became impatient; the "bubble" burst, and the index plunged from approximately 1,000 to the 130–150 range. From 2004 until 2008, the index remained volatile, ranging from lows in the low 100s to highs near 700.

The global economic crisis that began in 2008 exacerbated the industry's challenges as stock prices continued to tumble and many firms were forced to close their doors. When the Japan Biotech Association last updated its list of privately held Japanese biotech companies in 2007, it identified 586 private companies — we estimate that that number has now fallen well below 500.

The Japanese Government has invested considerable effort into building the industry, injecting funding, introducing administrative changes and streamlining regulatory structures. In 2002, the Biotechnology Strategy Council was established with the aim of growing the biotech market from ¥1.3 trillion (US$14.3 billion) in 2001 to ¥25 trillion (US$276.2 billion) in 2010, as well as creating one million new biotech jobs. The challenges of the intervening years have delayed the achievement of this goal — or, frankly, getting anywhere close. Nevertheless, the Government continues to encourage investment in key technology industries, including biotech, as described below.

Financing

A persistent challenge for Japan's biotech industry has been, and still is, raising capital. The size of VC investments across all industries in Japan is less than a fifth that of the US or Europe, and investments on a per-company basis in Japan pale in comparison to the West. According to a 2006 survey by the Venture Enterprise Center, created by Japan's Ministry of Economy, Trade and Industry, investments per company across all industries in Japan averaged ¥83 million (US$916,000), far below the average of ¥1.04 billion (US$11.4 million) in the US and ¥450 million (US$5 million) in Europe.

The financial crisis made the venture capital investing situation even more challenging. With the uncertainty in the global markets throughout 2009, investors became even more selective in their investment decisions, and venture capital investment across all industries reached its lowest level in 10 years. Venture capital firms have remained reluctant to provide new investment because of the low returns from IPOs. According to a report by the Japanese Venture Capital Association (JVCA), members' investments in 2009 were 30% lower than in 2008. Also, most of the biotech companies are considered too immature (often just a university professor with ¥10 million to invest in a novel technology), and there is not a large contingent of experienced venture capitalists with an established vetting process to identify the highest-potential prospects.

Japanese biotech IPOs, 2009

Company	Amount raised	IPO share price	Share price on 31.12.2009
JCL Bioassay	¥386 million	¥600	¥671
Tella Inc.	¥285 million	¥310	¥1,160
CanBas Co. Ltd.	¥1.2 billion	¥2,100	¥1,432
D. Western Therapeutics Institute	¥870 million	¥290	¥211

Source: Ernst & Young and TokyoIPO.com

In 2008 and 2009, the IPO market – across all industries in Japan – also hit historic lows. Between 2003 and 2007, Japan had averaged more than 100 newly listed companies a year across all industries. In 2008, the number of IPOs across all industries plummeted by 60%, and there were only three IPOs of biotech companies. In 2009, the number of industry-wide IPOs fell further, to 19. However, biotech IPOs held relatively steady at four – accounting for a remarkable 21% of all Japanese IPOs during the year.

In March 2009, JCL Bioassay, a contract research organization established in 1984, completed its initial public offering, raising ¥386 million (US$4.2 million). Tella, established in 2004, provides technology and support services for immune maximizing therapy for cancer to contract medical institutions. Tella raised ¥285 million (US$3.1 million) in its March 2009 IPO. In September 2009, CanBas, which is engaged in the research and development of anticancer drugs that will have minimal impact on normal cells, raised ¥1.2 billion (US$13.2 billion). The final 2009 Japanese IPO to close was D. Western Therapeutics Institute, which raised ¥870 million (US$9.6 million) in an October transaction. The company's drugs include anti-thrombotic medicine, a therapeutic agent for glaucoma, an anticancer drug, a therapeutic agent for high blood pressure, a protective agent for nerve cells, therapeutic agent for thrombosis and therapeutic agent for atherosclerosis.

As we go to press, CellSeed Inc. debuted as the first Japanese biotech IPO for 2010, raising a healthy ¥2.07 billion (US$22.8 billion) in March.

Because of the potential of the biotech market in Japan, efforts to stimulate this industry continue. In July 2009, the Tokyo Stock Exchange and the London Stock Exchange launched the TOKYO AIM, which targets professional investors in Asia and will be the Japanese equivalent of the UK's Alternative Investment Market. So far, the majority of shareholders of Japanese biotech companies have been individual investors, who often engage in speculative trading. TOKYO AIM could help to make the biotech sector more mature by attracting more stable, long-term investment by professionals. TOKYO AIM provides a new funding option for growing companies in Japan and Asia, while creating new investment opportunities for Japanese and international professional investors. Tokyo Stock Exchange Group, Inc., is the majority shareholder in the initiative, holding 51% of the shares, while the London Stock Exchange plc stake is 49%.

Also in July, a unique public-private partnership, the Innovation Network Corporation of Japan (INCJ) was unveiled (see *A closer look* on the following page). Leveraging the rich history of Japan's technological prowess and its global leadership in patent productivity, the INCJ (or Sangyo Kakushin Kikou as it is known in Japanese) will provide financial, technological and management support to next-generation businesses. The organization will also advocate "open innovation," which is expected to accelerate the development of new concepts and technologies by promoting collective thinking outside the walls of universities, start-ups and even established corporations.

The INCJ is capitalized at ¥90.5 billion (US$998.7 million), with the Japanese Government contributing ¥82 billion (US$904.9 million) and 16 leading private corporations providing the remaining ¥8.5 billion (US$93.8 million). According to the Japanese External Trade Organization (JETRO), these corporations include the Development Bank of Japan and Shoko Chukin Bank Limited as founding partners, which will invest approximately US$10 million and US$5 million, respectively. Other companies, which will also each invest approximately US$5 million, include Asahi Kasei Corporation, Osaka Gas Co., Ltd., Sharp Corporation, Nippon Oil Corporation, Sumitomo Chemical Co., Ltd., Sumitomo Corporation, Sumitomo Electric Industries, Ltd., Takeda Pharmaceutical Company Limited, Tokyo Electric Power Company, Inc., JGC Corporation, Panasonic Corporation, Hitachi, Ltd., The Bank of Tokyo-Mitsubishi UFJ, Ltd., and General Electric Company.

The INCJ will be established for 15 years, and the Government has also committed up to a total of ¥800 billion (US$8.8 billion) for further INCJ investments over this period,

giving the corporation an investment capability of approximately ¥900 billion (US$9.9 billion) over its 15-year tenure. With a key stake in funding promising intellectual property and early-stage technologies, we estimate approximately 10% of the fund will be targeted for early-stage biotech investment.

Mergers and acquisitions

After a flurry of acquisitions in 2007 and 2008 by Japan's established pharmaceutical companies, there was somewhat less Japanese big pharma M&A activity in 2009, mirroring a global trend. In September 2009, Dainippon Sumitomo acquired Massachusetts-based Sepracor for about US$2.6 billion – a 28% premium, and rivaling the multibillion-dollar acquisitions of foreign companies by Japanese pharmas such as Eisai, Takeda and Daiichi Sankyo in recent years. The deal gives Dainippon an expanded presence in the US, a market where it has historically had a small footprint, as it gears up to submit a new

A closer look

Yuji Anzai
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Funding innovation

Before the global financial crisis, Japanese biotech companies had relied on venture capital and IPOs to raise cash. But now, IPOs are not readily available and venture capitalists have become reluctant to invest. As a result, biotech companies have turned to big pharma for investment capital, but those opportunities are not available to many companies. Alternatively, many biotechs have explored M&A opportunities with other biotech companies to strengthen their respective pipelines and financial positions, but there have been few successful mergers to date. With Japanese biotech companies running low on options, the Japanese Government launched a new initiative in July 2009.

Known as the Innovation Network Corporation of Japan (INCJ, or Sangyo Kakushin Kikou in Japanese), the organization's main focus is on improving access to funding for underdeveloped industries – such as biotech – that are critical to the country's economy. As Kimikazu Nomi, INCJ's CEO stated in the press release that introduced the INCJ, "... [T]he INCJ is set to drive industrial innovation and social advances by enhancing the commercialization of promising technologies as well as intellectual property assets, some of which may be currently underutilized or even dormant."

It is worth noting that the INCJ is recruiting a wide range of experts from private equity funds, VC funds, financial institutions and technological and academic institutions. CEO Kimikazu Nomi was the former Chairman of Aozora Bank and COO Haruyasu Asakura was the former Managing Director at Carlyle Japan. Hiroyuki Yoshikawa, former President of the University of Tokyo, has been appointed as the Chairman of the INCJ's Industrial Innovation Committee.

Initially, investments will target six innovation-driven sectors: advanced materials, electronics, energy, environment, life sciences and machinery. The focus will be on supplying capital and management support to underutilized patents or intellectual assets at universities and private companies, providing new frameworks to develop technologies held by organizations such as venture firms and encouraging carve-outs for business units holding promising technologies.

The INCJ will draw on funding as well as management and technological expertise from the public and private sectors. Each investment will be thoroughly evaluated against standards set by INCJ's Industrial Innovation Committee, which will make the final investment decisions. By February 2010, more than 200 companies, including Toshiba Corp. and Alps Electric Co., have sought investment from the fund, according to a Bloomberg interview with COO Asakura. As the INCJ starts making its initial investment decisions, this will be an important initiative for Japanese life sciences companies to follow.

drug application for Lurasidone to the FDA in 2010. It also gets Sepracor's marketed products, including insomnia drug Lunesta and the asthma treatment Xopenex, as well as Stedesa, an epilepsy treatment awaiting marketing approval.

Takeda Pharmaceuticals, which made a splash a couple of years earlier with its US$8.8 billion acquisition of Millennium Pharmaceuticals, acquired another US-based company in May 2009, albeit for a much smaller purchase price. The company acquired California-based IDM Pharma for US$54.3 million. The deal allows Takeda to expand its oncology franchise through the acquisition of MEPACT, IDM Pharma's treatment for non-metastatic osteosarcoma.

In August, Hisamitsu Pharmaceutical acquired Miami-based Noven Pharmaceuticals for US$428 million. The US$16.50-per-share purchase price represents a 43% premium relative to Noven's average closing price for 90 days preceding the announcement. Once again, a key driver for the Japanese acquirer was establishing a US presence. In addition, Hisamitsu gained Noven's capabilities in transdermal drug development and intends to incorporate Noven's technologies into its drug development efforts.

Outlook

The worst of the global financial crisis appears to be over, but funding in the "new normal" remains challenging for many biotech companies across the world. In Japan, where venture capital for emerging companies was scarce even before the crisis, the funding challenge is truly stark. The Japanese Government continues to make the biotech industry a major priority, and efforts such as the INCJ could help, provided a significant enough portion of the funding goes to high-potential biotech companies. But Japan's biotech challenges run deeper, and it is not simply a matter of throwing money at the problem. In that regard, it is encouraging that the INCJ includes a vetting process and experienced leadership to increase the likelihood of funding truly innovative ideas with commercial potential. To make sure that Japanese innovations make the long journey to commercialization, efforts will need to be made to ensure that there is sufficient funding at every stage. With those changes, Japan might finally build a biotech industry that reflects its long tradition of technological and business leadership. ▶

Singapore year in review

Manufacturing a biopharmaceutical hub

Singapore continues to be a leading destination in Asia for the complex and technology-intensive manufacturing of biotechnology products, driven by the country's strengths in intellectual property protection, regulatory compliance and infrastructure and its highly skilled workforce. While the biotech sector in Singapore has not been unscathed by the economic downturn, it continues to attract increased investments from the Government and global biotech and pharmaceutical companies.

A manufacturing center

In recent years, leading biotech and pharmaceutical companies have set up several commercial manufacturing plants in Singapore. Those investments continued in 2009. In September, Switzerland-based Lonza began the construction of Asia's first cell-therapy manufacturing plant with an investment of S$40 million (US$27 million). Lonza plans to develop about 20 drugs across various therapeutic categories, including stroke, diabetes and heart disease in the plant. In August, Genentech Singapore (a member of the Roche Group) exercised its option to purchase another Singapore-based Lonza plant — a cell culture biologic manufacturing facility — for US$290 million plus milestone payments of US$70 million. The site has been manufacturing Genentech's blockbuster cancer drug Avastin under the terms of an agreement with Lonza since 2006. Genentech is also constructing a new bio-production site that will employ around 325 people to manufacture its macular degeneration treatment Lucentis. The plant is expected to be operational by 2010. In June 2009, GlaxoSmithKline opened a pneumonia vaccine manufacturing plant with an investment of S$600 million (US$415 million). Meanwhile, Baxter BioScience commenced construction of a biopharmaceutical manufacturing plant for ADVATE, a recombinant therapy for hemophilia.

Singapore is moving toward becoming a global leader in microarray manufacturing with US-based Illumina announcing the establishment of a US$20 million global manufacturing site in the city-state. Singapore currently accounts for more than half the global manufacturing capacity for microarrays, a technology largely used in biopharmaceutical research and diagnostics.

Growing R&D strengths

Singapore has also made strong efforts to attract R&D-intensive biomedical companies. After the completion of the first phase of a dedicated biomedical sciences R&D hub named "Biopolis" in 2004, the country has developed an integrated countrywide research network connecting research institutes at the Biopolis with leading medical institutes, public hospitals and investigational medicine units.

Singapore is an attractive R&D location because of its sound regulatory framework and adherence to global standards of safety, quality and efficacy. In January 2010, Singapore was added to the Organization for Economic Cooperation and Development's (OECD) "Mutual Acceptance of Data" framework under which data generated in preclinical trials in compliance with good laboratory practices is acceptable in 30 OECD and non-OECD member states. Meanwhile, the World Economic Forum's *Global Competitiveness Report 2009–2010* has given Singapore the top rating for intellectual property protection.

The year saw some examples of global biotechnology companies collaborating with state-run institutes on research initiatives. In March 2009, US-based FORMA Therapeutics collaborated with Singapore's Experimental Therapeutics Center to discover novel compounds based on FORMA's transformative chemistry platform. FORMA has also established its first overseas laboratory in Nanyang Technological University. Meanwhile, Singapore Immunology Network, a research consortium under Singapore's Agency of Science, Technology and Research, has partnered with two European biotech companies — Humalys SAS and Cytos Biotechnology — to develop antibodies targeting viruses prevalent in Asia, including hand, foot and mouth disease.

The global recession

The global economic slowdown has exacerbated the challenge of raising funds for the biotechnology industry in Singapore, where local financing options are limited and the industry has to largely depend on investments from global players. With venture capital and equity market investments drying up for most biotech companies, the Government of Singapore made concerted efforts to help the industry stay afloat. The Government introduced a "jobs credit scheme" in its 2009 budget to provide companies with cash grants to help retain employees during the downturn.

As in other parts of the world, the challenging capital situation has heightened the focus on extracting more value from existing assets and capabilities as well as on acquiring assets of ailing biotech companies. In October 2009, Singapore-based vaccine research player SingVax and US-based Inviragen merged to integrate their vaccine pipelines that are focused on infectious diseases prevailing in developing nations. The merged company also raised a US$15 million equity investment from a syndicate of private equity and venture investors. In July 2009, Transcu Group acquired a 45% equity interest in the Japanese Biomass Technology Company for a total consideration of ¥27 million (US$277,560). Biomass Technology Company has developed capabilities to produce biofuels from inedible biomass without fermentation.

Outlook

Cost advantages, best-in-class infrastructure and strong Government investments have made Singapore an attractive manufacturing location for multinational drug companies. However, cross-country cost advantages tend to be short-lived. Singapore has been sweetening the pot with large tax incentives, which may also prove unsustainable in the longer term. To take its success to the next level, the city-state will need to bring its focus and resources to fostering homegrown innovation. ▶

New Zealand year in review

A new pragmatism

The biotechnology industry in New Zealand has long faced some stiff challenges, including geographic isolation, a small domestic market and relatively sparse venture capital. Those challenges have been exacerbated by the global recession. As capital for the industry has shrunk around the world in the new normal, the New Zealand companies are often responding with pragmatic approaches to overcome obstacles. Investors are more focused than ever on achieving short-term returns. Meanwhile, biotech companies are exploring creative ways to develop new products, increased partnering at earlier stages, faster paths to commercialization and new ways to grow exports. The increased focus on pragmatic approaches has also been accompanied by some supportive Government initiatives.

Venture capital

Venture capital funding, which had fallen sharply in 2008, declined even further in 2009. Pragmatism forced venture firms – many of which are coming to the end of their first vintage – to allocate resources to sustaining existing portfolio companies. In 2009, only 16% of the total venture and mid-market private equity investment went to the health/biosciences segment – a sharp decline from the 52% share that the sector attracted in the previous five years.

This fall in venture funding, combined with a weak capital market, has motivated New Zealand biotech companies to seek funding and alliance partners beyond their national borders, in Australia, the US and other markets.

Angel investment

While local fund managers have had difficulty demonstrating adequate returns, a significant market has emerged for angel investment. According to the February 2010 issue of *Young Company Finance* published by the New Zealand Trade and Enterprise Escalator, the New Zealand Venture Investment Fund Limited, the New Zealand Private Equity & Venture Capital Association and Angel Association New Zealand, angel investors are playing an increasingly significant role in financing start-ups, with more than NZ$50 million (US$31.8 million) invested in 2009, a 72% increase over the previous 12-month record of NZ$29 million (US$18.4 million). These entities, supported by angel investors, represent part of the biotechnology company pipeline, but the real challenge facing the industry is ensuring access to sufficient investment capital for future development. Of the NZ$50 million (US$31.8 million) invested last year, NZ$20 million (US$12.7 million) went to first-round investments – the highest annual dollar value of investment into new companies.

Inbound investment

The New Zealand limited partnership (LP) regime, introduced in 2008, allows foreign investors to avoid any New Zealand tax liability from investing in an LP, subject to the LP's extent of business activities. (For details, refer to the New Zealand article in last year's *Beyond borders*.) This, together with the country's absence of a capital gains tax regime, offers an attractive proposition. However, New Zealand continues to have difficulty attracting foreign capital, and this has been exacerbated, in the case of biotechnology, by the international flight from higher-risk investments that occurred following the financial crisis.

Company formation and commercialization

In February 2010, Statistics New Zealand issued the results of its 2009 survey of the New Zealand bioscience industry. This survey indicated an increase of 25% in bioscience organizations from the 2007 level. The largest segment was innovative foods and human nutrition (comprising 44% of companies), followed closely by human biomedical science and drug discovery.

Remarkably, 58% of those surveyed plan to commercialize at least one new or significantly improved bioscience product in the next two years. The emphasis on bringing products to market quickly – often by focusing more on areas that do not require lengthy clinical trials or other regulatory barriers – is another indicator

of today's increasingly pragmatic industry. For example, Comvita, a biotech business created to exploit the health benefits of manuka honey, is continually researching and bringing new products to market.

Partnerships and alliances

Many New Zealand biotechnology companies partner and share information with other local and foreign organizations for product, process development or research. Aquaflow Bionomic Corporation is working with US-based Honeywell to develop technology that enables the harvesting and refining of wild algae to create biofuels (For more on biofuels, see the roundtable article "Embracing the future" on page 98). Other applications of the innovative technology, such as carbon sequestration, are also being explored.

The growing trend of partnering is gathering momentum, particularly with universities and research institutions. The University of Auckland Institute for Innovation in Biotechnology — built in 2009 and the first such incubator in New Zealand brings together academics and industry partners from biotech and pharma in one location. Partners draw on the expertise of internationally recognized academics through collaborations or contract research. The Government-supported institute aims to increase collaboration between universities and industry, lower entry barriers for newcomers and advance New Zealand's biotechnology workforce. A number of venture-backed businesses are already based in the institute or planning to set up operations, including CoDa Therapeutics and Androgenix.

Government support

A new Government was elected in 2008, and despite eliminating the R&D tax credit, it maintains a significant focus on innovation and biotechnology. The challenge is to identify ways to improve the effectiveness of ongoing investment in science, technology and innovation, particularly biosciences.

In encouraging development, the Government not only gave Living Cell Technologies (LCT) approval to enter Phase II trials of DIABECELL-encapsulated porcine islets for treating insulin-dependent diabetes, but also provided NZ$7.8 million (US$5 million) in grants to the company to fund the clinical trials. Interestingly, LCT has also licensed its patented encapsulated technology to non-competing partners to help fund ongoing trials.

In March 2010, a Government-appointed taskforce issued recommendations for improving the performance of the Government-funded Crown Research Institutes (CRIs). The report recommended significant changes to the way CRIs are operated to provide greater funding certainty for long-term projects. It also included measures to encourage technology transfer and boost spin-offs of businesses from CRIs, particularly in health care, agricultural biotech and food technology.

Outlook

While the Government interest in the industry is a positive step, the growth of New Zealand biotechnology will also be driven by better offshore product marketing, growth in sectors such as biofuels and foods, and the ability to serve the needs of other emerging markets.

For example, China — a country that has been actively investing in New Zealand agriculture — is showing an interest in New Zealand biotech, attracted by the country's high standards of education and strong product/food safety systems.

New Zealand biotech companies are taking a fresh look at business models, deal structures, financing, partnering and joint ventures. They are looking for investors to develop their products further and provide market entry into Europe and the US. They are also working to get products to market sooner. Many pipeline products are at a stage in the life cycle where they can be licensed to offshore organizations to create a revenue stream to fund further R&D. Continued growth will depend on companies' abilities to follow through on these creative and pragmatic solutions. ▶

Brazil year in review

Fueling the future

Like many emerging economies, Brazil is progressing from an imitator to an innovator. Its fairly young biotechnology industry is likewise evolving — and actively so. However, the country will need to tackle obstacles such as regulatory barriers and limited access to capital from private equity.

A leader in agricultural biotech

According to a 2009 survey by the International Service for the Acquisition of Agri-biotech Applications (ISAAA), Brazil has overtaken Argentina to become the world's second-largest user of genetically modified (GM) crops. GM soy is Brazil's leading GM crop (71% of the crop's planted area), followed by GM corn (30%) and GM cotton (16%). Recent approvals of GM crop varieties include Monsanto's GM cotton, Bollgard II, which was approved for commercial use in May 2009, as well as two new Monsanto varieties of pest/herbicide-resistant GM corn, which were approved in September. Switzerland-based Syngenta received approval to cultivate two varieties of its insect-resistant GM corn, while Bayer received approval for two varieties of GM soy.

In addition, regulators cleared the experimental planting of 15 new GM seed varieties in 2009. Of these, 12 corn, cotton and soy varieties are expected to be tested by Monsanto, two corn varieties by Dow AgroSciences and one sugarcane variety by Brazil-based Alellyx Applied Genomics.

A biofuels pioneer

As home to one-third of the world's sugarcane plantations, Brazil has emerged as a global frontrunner in the development and adoption of biofuels as an alternate source of energy. The country currently produces around 25 billion liters (6.5 billion gallons) of ethanol annually from sugarcane and plans to increase production by as much as 150% by 2017.

In June 2009, Brazilian mining giant Vale announced plans to invest in the construction of a biodiesel unit in partnership with Biopalma da Amazônia SA. Similarly, oil major Petroleo Brasileiro, or Petrobras, unveiled a five-year plan to invest US$3.3 billion and make strategic acquisitions to enhance its capabilities in this high-potential segment.

Brazil's strong reputation in biofuels has also led to partnerships with several key industry players from outside the country, including Israel-based Evogene, a leader in plant biotechnology, and Novozymes, a Denmark-based enzymes manufacturer. US-based Amyris Biotechnologies is also building a strong presence in Brazil's biofuels market. In December 2009, it reported letter-of-intent agreements with three Brazilian companies — Açúcar Guarani, Bunge Limited and Cosan — to produce ethanol and high-value chemicals; and in April 2010, it announced a joint venture with the São Martinho Group, one of the largest sugar and ethanol producers in Brazil.

Deals

To develop innovative capabilities and tap high-potential international markets, Brazilian biotech companies have entered a number of collaborative agreements with foreign life sciences players. Deals have primarily been in the biofuels and human health segments.

In December 2009, leading Brazilian biopharmaceutical company EMS Sigma Pharma announced plans to form a Brazil-based joint venture with Cuban pharmaceutical company Herber Biotec. Under the terms of this agreement, Herber

Biotech will provide the technology and intellectual property developed by Cuba's Center for Genetic Engineering and Biotechnology, and EMS Sigma Pharma will develop production capabilities while providing infrastructural and logistical support for the global distribution of the resultant products. EMS Sigma Pharma entered another agreement with two Shanghai-based laboratories, Biomabs and Guijian, to gain a technology platform for the production of the rheumatoid arthritis treatment etanercept. Under this agreement, the company is also expected to acquire a technology platform to manufacture five more monoclonal antibodies in the future.

FK Biotecnologia entered an agreement with Canada-based ZBx Corporation to conduct the clinical development of FK's pipeline vaccine for prostate cancer. FK plans to initiate Phase III trials to seek marketing approval of this vaccine by 2010. Two other Brazilian companies, Biocancer and Genoa Biotecnologia, also have anticancer vaccines in clinical trials, and the companies are currently seeking partnerships to further develop these products.

Financing and investments

There are relatively few Brazilian venture-capital firms that are actively investing in high-risk biotechnology. Consequently, Brazilian biotech companies largely rely on Government grants and income streams from services. Currently, the Government accounts for around 65%–70% of total R&D expenditures.

Stem cell research has been attracting investments from the Government and private players. In February 2009, the Government announced plans to construct eight laboratories for stem cell research. The National Bank for Economic and Social Development (BNDES) and Brazil's Ministry of Health, Science and Technology have funded the project with a total investment of R$23.6 million (US$12.5 million).

Several global life sciences companies entered Brazil in 2009 to tap the domestic market's potential and leverage its low-cost advantages. Belgium-based UCB collaborated with AstraZeneca to commercialize UCB's PEGylated anti-TNF alpha drug, Cimzia, in Brazil. In another similar agreement, BurnsAdler Pharmaceuticals — a US-based distributor specializing in marketing products throughout Latin America — announced plans to market Three Rivers Pharmaceuticals' Hepatitis C infection therapy, Infergen (type 1 interferon alpha), in Brazil and Chile.

Roche has also made significant strides in the Brazilian biopharmaceutical market. During 2009, the company launched the chronic renal anemia drug Mircera and the rheumatoid arthritis drug Actemra in the Brazilian market. Roche's subsidiary in Brazil, which is being developed as an export-oriented arm to provide low-cost drugs to European markets, invested US$50 million in clinical research in 2009. It also began production at its US$85 million plant in Rio de Janeiro.

Accompanying the flurry of global inbound investments were investments by domestic players in production and marketing capabilities. São Paulo-based pharmaceutical company Uniao Quimica announced plans to invest R$150 million (US$85.5 million) to set up an insulin-manufacturing plant in Brasilia. Another Brazilian pharmaceutical company, Cristalia, has begun construction of a new biotechnology unit in Rio de Janeiro to manufacture human growth hormones and interferon. The company has already invested R$20 million (US$35.5 million) in the project and plans to invest an additional R$25 million (US$44.3 million) in the new facility.

Over the past few years, leading global contract research organizations have been building operations in Brazil to benefit from the country's cost advantages, strong patient pool and quality resources. US-based Covance entered the Brazilian market with the launch of a new clinical development office in São Paulo. According to Covance, the new facility is expected to support personnel in Brazil, Central America and the Caribbean as well as the network of field-based clinical research associates. Another clinical development services provider, PharmaNet Development Group, also recently established an office in São Paulo to strengthen its Latin American presence.

Regulatory challenges

The regulatory structure of the Brazilian biotechnology industry is fairly complicated, with different laws and regulators governing various segments of the industry. Brazil's National Health Surveillance Agency (ANVISA) regulates health products, including those produced using biotechnology techniques. ANVISA's General Office of Drugs and the General Office of Research, Clinical Trials, Biological, and New Drugs holds the authority to approve clinical trials conducted in the country. In addition, the National Commission for Ethics in Research (CONEP) focuses on ethical considerations. The Council for Management of Genetic Patrimony (CGEN), which is affiliated with the Ministry of Environment (MMA), protects biodiversity. And two separate bodies — the National Biosafety Council (NBSC) and the National Biosafety Technical

Commission (CTNBio) — determine the bio-safety of GM products and regulate stem cell research and commercialization.

Conflicting rules and the lack of a consolidated industrial policy have created challenges for companies operating in the country. Complex regulatory procedures have also often led to long delays in gaining product approval. However, the Government has recently made efforts to streamline the regulatory process to make it more efficient and investor-friendly, with most of the policy improvements centered on the GM crop industry. In 2008, for instance, the Government gave CTNBio final authority on all approvals of GM products, addressing the overlapping functions of NBSC and CTNBio.

Progress has also been made in addressing the protection of intellectual property (IP) rights related to biotechnology. The Government is evaluating an option to grant IP protection for biological material, but only for Brazilian researchers. The Brazilian Parliament is also considering a proposal to eliminate the use of secondary or polymorph-related patents on various drug substances to strengthen the IP protection environment in the country.

Outlook

Brazil's biotechnology industry has evolved considerably during the last decade and is fostering the formation of innovation-focused biotechnology companies. The sector is being boosted by major Government initiatives, such as the Biotechnology Development Policy (PDB) and a 10-year, US$4.0 billion biotechnology development program. Brazil has been attracting considerable foreign investment, and domestic companies are strengthening their research and manufacturing capabilities while enhancing their marketing strength in foreign markets. However, the country's infrastructure and regulatory processes are still evolving, and continued focus will be required to maintain growth. ▶

Malaysia year in review

A strategic focus on biotech

Malaysia's budding biotechnology industry has been a key strategic focus for the nation's policy-makers and business community in recent years. Like many emerging markets, its strategy has often hinged on leveraging areas of competitive advantage, such as its extraordinarily rich biodiversity. These strategic investments continued in 2009.

Government investment

The Malaysian Government has allocated RM 2 billion (US$571.4 million) under the Ninth Malaysian Plan (2006–10) to fund the development of the industry. Between the launch of the National Biotechnology Policy (NBP) in 2005 and late 2009, the Government estimates that the industry has received cumulative investments of RM 4.5 billion (US$1.3 billion), of which 58% came from the Government and the remainder from the private sector. The industry continues to attract strategic investments, with the Government allocating RM 1.3 billion (US$371.1 million) for biotechnology development under the First and Second Stimulus Packages in 2008 and 2009.

Malaysian Biotechnology Corporation (BiotechCorp, the lead agency responsible for implementing the NBP) estimates that the number of biotech companies has increased threefold since 2005, with 41% of existing companies involved in agricultural biotechnology (reflecting the country's traditional strengths in agriculture), followed by 38% in medical biotechnology and the remaining 21% in industrial biotechnology.

Sustainable funding

It is no secret that bringing biotechnology products to market is a long, expensive and high-risk process. In the West, there has traditionally been a thriving ecosystem of investors that provide multiple rounds of funding as companies move along the biotechnology industry value chain. In Malaysia, however, existing private funds for biotechnology are inadequate to meet the developmental goals set out in the NBP.

While there are approximately 38 VCs that identify biotechnology as one of their focus investment areas, only two firms — SpringHill BioVentures and First Floor Capital — have invested actively in biotech companies. In total, the VCs have invested close to RM 251 million (US$71.7 million) in life sciences during the last three years (2006–08), but life sciences investments as a share of investment across all industries declined from 24% in 2006 to 18% in 2008. Furthermore, only 31% (US$22.6 million or RM 79 million) of the investment between 2006 and 2008 went to Malaysian companies. Attracting venture capital clearly remains a challenge for Malaysian biotech companies. And this is especially so when it comes to second-round funding for pre-commercialization and commercialization activities.

The Government is attempting to increase investor confidence and attract greater private-funding participation. This includes continuing to allocate funds for soft loans and proposing a new venture fund that would aim to attract greater participation of foreign VCs specializing in biotechnology.

Deals

In late 2008 and early 2009, Malaysia's Holista Biotech acquired CollTech Australia, a Perth-based company listed on the Australian Stock Exchange, through a reverse takeover. As part of the transaction, CollTech issued 770 million shares to Holista, giving Holista shareholders about 70% of the voting rights in CollTech and making Holista a subsidiary of CollTech. The two companies have strong synergies on the product front — CollTech specializes in ovine collagen products, and Holista focuses on natural products such as collagen.

BiotechCorp spearheaded the acquisition of four platform technologies with the intention of boosting innovation: two platform technologies acquired for health care, the nanotechnology platform from Nanobiotix and the DotScan antibody microarray diagnostic platform technology from Medsaic; the Marker Assisted Selection

platform technology from DNA LandMarks for agriculture; and the Supercritical Fluid technology with applications for extraction and particle formation from Feyecon for the industrial biotechnology sector.

Bridging talent gaps

Biotechnology companies have very specific human-capital needs, and fostering the right skills has been a challenge in Malaysia. Although the country's Institutes of Higher Learning are the key institutions developing human resources for the biotechnology industry, BiotechCorp supplements the effort through several programs. These include the Biotechnology Entrepreneurship Special Training (BeST) program and Post-Doctoral Research Program. BiotechCorp has also designed programs through collaboration with National Business Incubator Association (NBIA), California Institute of Quantitative Bioscience (QB3) and Stanford University's Office of Technology Licensing.

Going green

With its agricultural foundation in commodity crops such as oil palm, Malaysia is well positioned to take advantage of the global focus on developing environmentally friendly technologies. It can leverage its abundant biomass (e.g., palm oil waste and waste from other commodity crops) to provide a readily available, sustainable and economical source of feedstock for the production of biofuel. Palm oil biowaste can also be used in the production of organic biofertilisers and the research and utilization of effective microbes from Malaysia's rich biodiversity.

SuccessNexus, a Malaysian company, uses multi-feedstock technology to convert oil-based products and waste into biodiesel and glycerine. The company has developed a mobile refinery that can be transported into remote rural areas to convert oil-based waste into biodiesel. Other examples of cleantech-focused local companies include Return 2 Green and Bio Green Bags, which use biotechnology processes to develop biodegradable and compostable disposal products out of agricultural waste.

Outlook

Malaysia's rich tropical biodiversity and abundant natural resources provide a key differentiator as investors and businesses everywhere focus on green technologies. The Government continues to make investments, but attracting private-sector investors will become increasingly important for building a sustainable biotechnology industry. As such, it will be critical for Malaysian companies to focus on accelerating paths to commercial success. In addition, there is a need for foreign collaboration for technology and knowledge transfer especially in the development of the health care and industrial biotechnology sectors. The Bio-XCell strategy is part of the effort to attract global companies to set up operations in Iskandar Malaysia, Johor. Bio-XCell is a biotechnology ecosystem that is currently being developed through a public-private partnership between BiotechCorp and UEM Land Holdings. It is intended to be a hub with special focus on industrial biotechnology, particularly in green technology, and it will have ready-built and customized commercial-scale shared facilities that are available for lease to interested local and global companies. ▶

A transformational year

Industry performance

Financial performance

A transformational year

It is fair to say that 2009 has been a year like few others. Around the world, companies, households and governments struggled as they were buffeted by the deepest recession in more than seven decades. The biotechnology industry was not immune to these developments, and the economic crisis had a palpable impact on the sector's financial performance.

For both the global economy and the global biotech industry, the impact was not uniform. Indeed, the emerging biotech sectors in China and India — two countries that continued to grow even as most economies slipped into recession — were not negatively impacted by the downturn.

This article, and the rest of this section of *Beyond borders*, focuses on the performance of the biotech industry in the world's *established* biotech centers: the US, Europe, Canada and Australia. The industry's performance in emerging markets, including China and India, is discussed in the *Country profiles* section. (Since biotech sectors are still emerging in these markets, our discussion of them differs from the one here in relying on both qualitative and quantitative indicators.)

Across the four major biotech centers, the business environment became considerably more challenging in 2009. While the industry raised healthy amounts of capital in aggregate, the stark reality that many biotech companies face in the "new normal" is that funding is harder to come by. Venture capitalists have become more discriminating, and the IPO markets have largely been closed to new companies seeking to raise funds from public investors. (For more on the financing picture, see the *Financing* article, "A higher bar.")

While all companies need capital, there are few businesses that have biotech's combination of huge capital needs and long paths to commercial sustainability. Many biotech companies have therefore had to take strong measures to survive. To raise funds and reduce cash burn, large numbers of firms have restructured their businesses, laid off workers, sold non-core assets and shelved R&D projects. In many cases, this has also included increased reliance on conducting R&D or manufacturing activities in lower-cost locations. While the potential cost savings from such measures can be attractive, companies consider a variety of strategic factors when making location decisions. The tax implications of cross-border operations, for instance, are discussed in *A closer look* on the following page.

If the biotech industry is unique in its capital needs, it is also unique in its ability to survive capital droughts. Biotech companies — and the serial entrepreneurs frequently at their helm — have survived several funding famines by responding creatively to shifting market conditions. Given the depth and systemic reach of this recession, however, many observers expected a sharp drop in the number of companies. So far, those fears have largely not been borne out. While we expect continued attrition and the lack of a robust IPO market to further trim the ranks of biotech companies in the year ahead, the reduction in the number of public companies in 2009 was not as significant as anticipated. There were 622 public biotech companies in the established biotech centers as of December 2009, compared to 700 a year earlier — an 11% decline, well short of the 25%–33% decrease that many analysts were expecting.

The global recession did, however, have a more immediate impact on the financial results of public biotech companies. Across the four established biotech centers, the numbers (and the story behind the numbers) were remarkably consistent. The first of these impacts was on the top line of the income statement. The industry's revenues fell by 9%, from US$86.8 billion in 2008 to US$79.1 billion in 2009. However,

Growth in established biotechnology centers, 2008–09 (US$b)

	2009	2008	% change
Public company data			
Revenues	79.1	86.8	-9%
R&D expense	22.6	28.7	-21%
Net income (loss)	3.7	(1.8)	-314%
Number of employees	176,210	186,820	-6%
Number of companies			
Public companies	622	700	-11%

Source: Ernst & Young
2009 financials largely represent data from 1 January 2009 through 31 December 2009.
2008 financials largely represent data from 1 January 2008 through 31 December 2008.
Numbers may appear inconsistent because of rounding.

the bulk of this decline was driven by Roche's acquisition of Genentech, which effectively absorbed one of the giants of the biotech industry into a big pharma company. Without this acquisition, the industry's revenues would have *grown* by 8%.

While this is undoubtedly much better than a 9% decline, it still represents a reduction from the growth rates the industry has been accustomed to seeing. For most of the last decade, the biotech industry has consistently delivered double-digit revenue growth, driven by strong product sales at the relatively small number of mature companies with commercialized products — including Genentech. That trend started to change in 2007, when revenue growth slowed somewhat in the US market in the wake of certain new safety-related warnings. In 2009, there was a similar slowdown in Europe as UK-based Shire — the largest company by revenues in the European market — faced what it called a "transformational year." Shire's revenue growth flattened when one of its leading products faced generic competition for the first time. While increasing generic competition and pricing pressure will continue to squeeze the industry's revenue growth in the new normal, it is worth noting that the slowdown in 2009 cannot fully be

A closer look

Bruce Bouchard
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Seeking efficiency: considerations when operating beyond borders

As biotech companies in the West look for efficiencies in the "new normal," many are increasingly drawn to outsourcing and overseas operations to drive revenue growth and to capture relative cost advantages. But operating beyond borders can have complex tax implications, which should be considered up front. While large pharmaceutical and biotech companies have been global for some time and have experience designing tax structures to minimize effective tax rates and take advantage of tax incentives in different jurisdictions, this is unfamiliar territory for many smaller biotechs.

Biotech companies expanding into new geographies may seek to emulate pharma-like tax strategies, while those that are already global will need to understand the risks and changing environment that impact their effective tax rates. Those still in the early stages of globalization should evaluate the feasibility of multinational structures, given the changing tax environment. They will also need to consider the political and economic stability of potential countries for location of facilities and availability of needed workforce.

At a time when the global recession has negatively impacted tax revenues, many governments are working more closely with each other to reduce the ability of companies to minimize taxes through cross-border transactions. Some jurisdictions have enacted legislation to restrict the ability to defer foreign profits by expanding economic substance and business purpose doctrines and by limiting the deductibility of worldwide interest expense and headquarter expenses.

Still, there are opportunities to minimize global tax rates by proactively managing the ownership and development of intellectual property rights on a worldwide basis. An important element of effective tax planning is the alignment of tax strategies with business activities and objectives. Many of these strategies take time to mature as intellectual property is developed, so it is important for early-stage biotech companies to proactively consider tax planning long before a product is ready for commercialization.

Global organizations, or those considering going global, should:

- Align the tax strategy with the business strategy
- Evaluate the systems and resources for managing tax risk
- Strategically manage tax issues
- Include global tax risk in corporate governance planning
- Stay current on tax policy and legislative developments

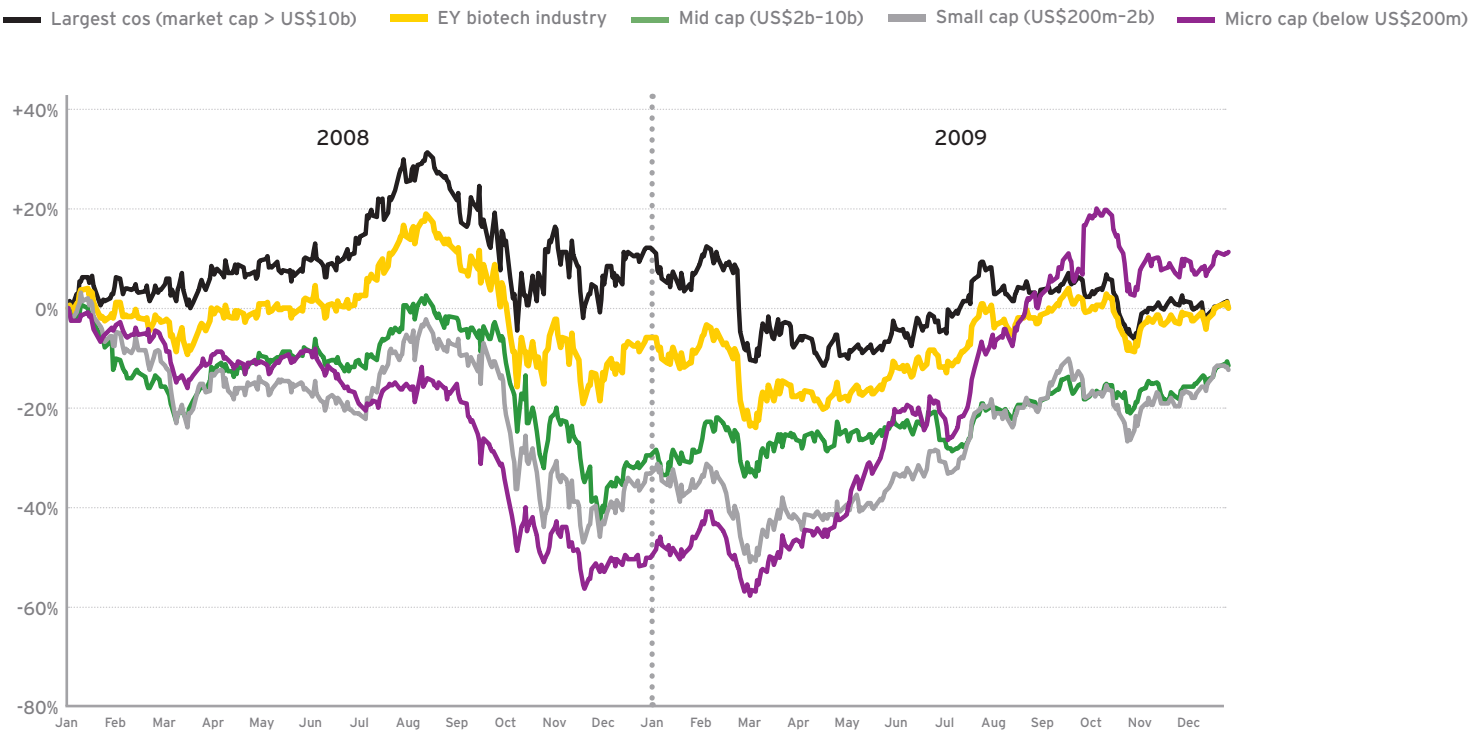
explained by developments at a few large companies. Even after controlling for such impacts, the revenues of the industry grew at a markedly slower pace in 2009 – reflecting, perhaps, a broader shift in market conditions.

The cost-cutting and restructuring efforts of biotech companies also had a visible impact on the industry's R&D spending and net income. As many biotech companies took extreme measures to reduce cash burn, R&D expenditures were often a casualty. After years of double-digit increases in R&D spending – which often grew at a faster clip than revenues – the industry's R&D expenditures declined by 21% in 2009. Biotechnology is, of course, a research-driven industry, and this is a potentially worrying development for the sector's continued growth. In seeking short-term survival, some companies may be hurting their long-term prospects.

Profitability, as many readers of *Beyond borders* know, is a measure we have been tracking and forecasting for some time. In 2005, we predicted that the US publicly traded industry would reach aggregate profitability by the end of the decade. Even as the US industry inched ever closer to that symbolic landmark with every successive year, the superheated M&A environment often took sizeable bites out of the sector's net income, when several successful, profitable biotech firms were acquired by big pharma buyers. For a couple of years, the US industry hovered around the breakeven point, narrowly missing the profitability mark in 2007 before barely squeaking through to the black in 2008. But Genentech's acquisition made a more than US$3 billion dent in the industry's net income, and we felt fairly certain that it would be many years before profitability returned.

Well, what a difference a recession makes! The US industry's net income skyrocketed from about US$400 million in 2008 to an unprecedented US$3.7 billion in 2009 – more than compensating for the loss of Genentech by a wide margin. In fact, the US industry was so solidly profitable in 2009 that it helped move the aggregate net income in established markets into the black for the first time as well – from a US$1.8 billion net loss in 2008 to a US$3.7 billion net *profit* in 2009. As discussed in the United States section below, a number

After declining in 2008, smaller companies recovered in 2009



Source: Ernst & Young, finance.yahoo.com
"EY biotech industry" represents the aggregate market cap of all US public biotech companies as defined by Ernst & Young.

of factors, including a change in accounting rules, contributed to the large uptick in US profitability, but cost reductions certainly played a significant role. It is also worth noting that, while increased profitability was most dramatically apparent in the US, the bottom line in each of the other established centers — Europe, Canada and Australia — improved significantly in 2009. Operating efficiency, it would appear, is an integral part of the new normal.

That drive for efficiency was also clearly visible in the industry's survival index, which measures the number of years of cash that companies have on hand based on their current cash burn. In 2008, the survival index had deteriorated considerably as many companies had a difficult time raising capital. But in 2009, thanks to the efforts to reduce cash burn (as well as the success some companies had in fund-raising transactions) the survival index bounced back in the US and Europe, though there was no appreciable improvement in Canada.

United States

As mentioned above, the financial results of the US biotechnology sector were skewed by the megadeal of the decade — the acquisition of Genentech by Roche. At the time of the transaction, Genentech accounted for more than 20% of the revenues of the US publicly traded biotech industry, so it is not surprising that the transaction had a sizeable impact on the industry's results.

The revenues of US public companies fell to US$56.6 billion in 2009, a 13% drop compared to 2008. After removing Genentech from the 2008 numbers, the industry's revenues would have instead *increased* by 10%; adjusting for Sepracor, the year's other significant acquisition would have raised the growth rate even further, to 12%. This is fairly consistent with 2008, when the industry's revenues grew by 8.4%, or 12.7% adjusted for significant acquisitions. In addition to the acquisition of Genentech, the industry's revenues were impacted by declining revenue at a couple of industry stalwarts: Amgen (which saw revenues decline because of a significant decline in sales of Aranesp, driven by a product safety-related label change that occurred in August 2008) and Genzyme (which was negatively impacted by manufacturing problems for Cerezyme and Fabrazyme).

R&D spending decreased by 24%, compared to a 20.5% increase in 2008. After adjusting for the Genentech acquisition, R&D expenditures would have still decreased by 13%. Companies reporting significant reductions in R&D spending included Amgen, Celgene and United Therapeutics. However, the trend was fairly consistent across the industry, with 64% of companies reporting reductions in R&D spending. In contrast, back in 2007, before the onset of the financial crisis, only 37% of US public companies reduced R&D spending during the year.

As mentioned above, the truly noteworthy development in the US industry was its profitability. The net income of publicly traded biotech companies increased from about $US400 million in 2008 to an unprecedented US$3.7 billion in 2009. This is all the more impressive given that the acquisitions of Genentech and Sepracor had removed US$3.9 billion of profits from the industry.

The remarkable uptick in profitability was driven by a combination of factors. The first of these is a seemingly arcane change in accounting rules, but one with significant implications for the biotech industry: the treatment of acquired in-process R&D (IPR&D). Large acquisitions by US biotech companies have typically resulted in hefty charges for acquired IPR&D — essentially the estimated fair value assigned to ongoing R&D projects acquired in a business combination. Given the active deal environment in recent years, the US industry's profitability has been lowered every year by these significant charges. In 2008, for instance, US biotech acquirers incurred about US$2.3 billion in acquired IPR&D charges, in the absence of which the industry would have been very comfortably in the black. Starting in January 2009, however, the accounting treatment of acquired IPR&D changed. Instead of reporting IPR&D as an expense on the income statement, US companies are now required to capitalize it as an asset, eventually amortizing the assigned value to expense. While the rule changes create several challenges for companies entering deals (see "Valuing milestones," by Michelle Mittelsteadt, on page 79 for a detailed discussion), the absence of acquired IPR&D charges gave an immediate boost to the industry's net income in 2009.

The reduction in the number of public companies also helped the industry's profitability, since the majority of companies that were acquired or ceased operations during the year were in a net loss position. In aggregate, these companies had racked up net losses of approximately US$850 million in 2008, and their removal boosted the industry's bottom line by a similar amount.

The sum of all these factors, however, is not sufficient to account for the magnitude of the increase in industry profits in 2009. Much of the difference came from one-time events such as asset sales, tax benefits, milestones and royalty payments as well as increased efficiencies at large numbers of companies across the industry. Noteworthy examples include industry leaders such as Amgen and Gilead, which

Selected 2009 US biotechnology public company financial highlights by geographic area (US$m, percent change over 2008)

Region	Number of public companies	Market capitalization 31.12.09	Revenue	R&D	Net income (loss)	Cash and equivalents	Total assets
Los Angeles/Orange County	14	60,596	15,211	3,266	4,128	3,221	41,330
	-18%	*-7%*	*-2%*	*-8%*	*21%*	*42%*	*7%*
New England	45	51,654	11,827	4,108	320	3,113	26,091
	-22%	*3%*	*-9%*	*-16%*	*-755%*	*-26%*	*1%*
San Francisco Bay Area	62	59,950	11,754	3,380	1,184	3,891	20,422
	-13%	*-60%*	*-50%*	*-49%*	*-58%*	*-59%*	*-48%*
San Diego	35	23,624	5,811	1,617	(589)	1,838	15,888
	-15%	*36%*	*49%*	*-2%*	*-38%*	*-9%*	*3%*
New Jersey	23	28,715	3,553	1,231	371	1,647	6,611
	-18%	*1%*	*18%*	*-24%*	*-115%*	*1%*	*5%*
Pennsylvania/Delaware Valley	12	8,435	2,808	704	(59)	2,731	7,024
	-20%	*0%*	*13%*	*-8%*	*-33%*	*135%*	*44%*
North Carolina	10	5,487	1,916	332	(51)	523	2,649
	-9%	*412%*	*343%*	*6%*	*-75%*	*53%*	*193%*
New York State	22	6,284	1,271	733	(291)	643	3,026
	-8%	*10%*	*18%*	*6%*	*-501%*	*-13%*	*3%*
Mid-Atlantic	21	11,076	1,254	652	(123)	1,209	4,460
	-5%	*123%*	*37%*	*-37%*	*-80%*	*142%*	*38%*
Utah	3	2,798	437	109	42	111	875
	50%	*-17%*	*-10%*	*-5%*	*162%*	*-52%*	*13%*
Pacific Northwest	16	6,401	289	460	(599)	806	1,814
	7%	*302%*	*33%*	*-9%*	*-6%*	*234%*	*124%*
Southeast	17	2,289	216	204	(185)	342	697
	-23%	*23%*	*-9%*	*-24%*	*-39%*	*-13%*	*-24%*
Texas	9	1,091	133	133	(133)	203	522
	-10%	*-15%*	*-3%*	*-28%*	*-6%*	*6%*	*2%*
Colorado	6	900	35	121	(205)	253	344
	-33%	*-1%*	*22%*	*-26%*	*-16%*	*73%*	*15%*
Midwest	10	541	24	80	(123)	128	177
	-9%	*-10%*	*55%*	*-29%*	*-20%*	*-8%*	*-16%*
Other	8	530	98	49	(13)	31	245
	-20%	*2%*	*-43%*	*-26%*	*-1445%*	*-30%*	*-5%*
Total	**313**	**270,371**	**56,637**	**17,179**	**3,675**	**20,688**	**132,174**
	-14%	***-21%***	***-13%***	***-24%***	***782%***	***-13%***	***-6%***

Source: Ernst & Young and company financial statement data
Percent changes refer to change over December 2008. 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

together improved their net income by about US$1 billion, as well as up-and-coming firms such as Human Genome Sciences and Jazz Pharmaceuticals.

Europe

Like their US-based counterparts, European biotech companies demonstrated considerable resilience in the economic downturn. The number of public companies decreased by only 4%, from 179 companies in 2008 to 171 in 2009 – a much smaller drop than most industry watchers had expected.

Revenues of publicly traded European companies grew from €11.0 billion in 2008 to €11.9 billion in 2009 – an 8% increase that was well below the 17% growth seen in 2008. While several of Europe's leading companies – including Actelion, Crucell, Elan, QIAGEN and Meda – continued to post double-digit revenue growth rates, UK-based Shire saw a significant slowdown on its top line. This was largely the result of the introduction of generic competitors to Adderall XR, its blockbuster drug for treating attention deficit hyperactivity disorder. Excluding Shire, Europe's other large companies – those with revenues greater than €200 million – saw their combined top line expand by a robust 14%. However, smaller public companies below the €200 million threshold saw revenues *decline* by 1%, dragging down the overall sector's performance.

As in the US, R&D expenditures failed to keep pace with revenue growth. European public companies' R&D expenditures were essentially flat, posting a modest 2% decrease in 2009. This was driven not by a few large companies, but rather by R&D cutbacks across much of the industry. Similar to the situation in the US, close to 60% of public companies reduced their R&D expenditures in 2009.

US biotechnology at a glance, 2008–09 (US$b)

	2009	2008	% change
Public company data			
Product sales	48.2	53.9	-11%
Revenues	56.6	65.1	-13%
R&D expense	17.2	22.6	-24%
Net income (loss)	3.7	0.4	782%
Market capitalization	270.4	340.7	-21%
Number of employees	109,100	120,300	-9%
Financings			
Capital raised by public companies	13.5	8.6	58%
Number of IPOs	3	1	200%
Capital raised by private companies	4.9	4.4	10%
Number of companies			
Public companies	313	366	-14%
Private companies	1,386	1,405	-1%
Public and private companies	1,699	1,771	-4%

Source: Ernst & Young
Data were generally derived from year-end information (31 December). The 2009 data are estimates based on January–September quarterly filings and preliminary annual financial performance data for some companies. The 2008 estimates have been revised for compatability with 2009 data. Numbers may appear inconsistent because of rounding.

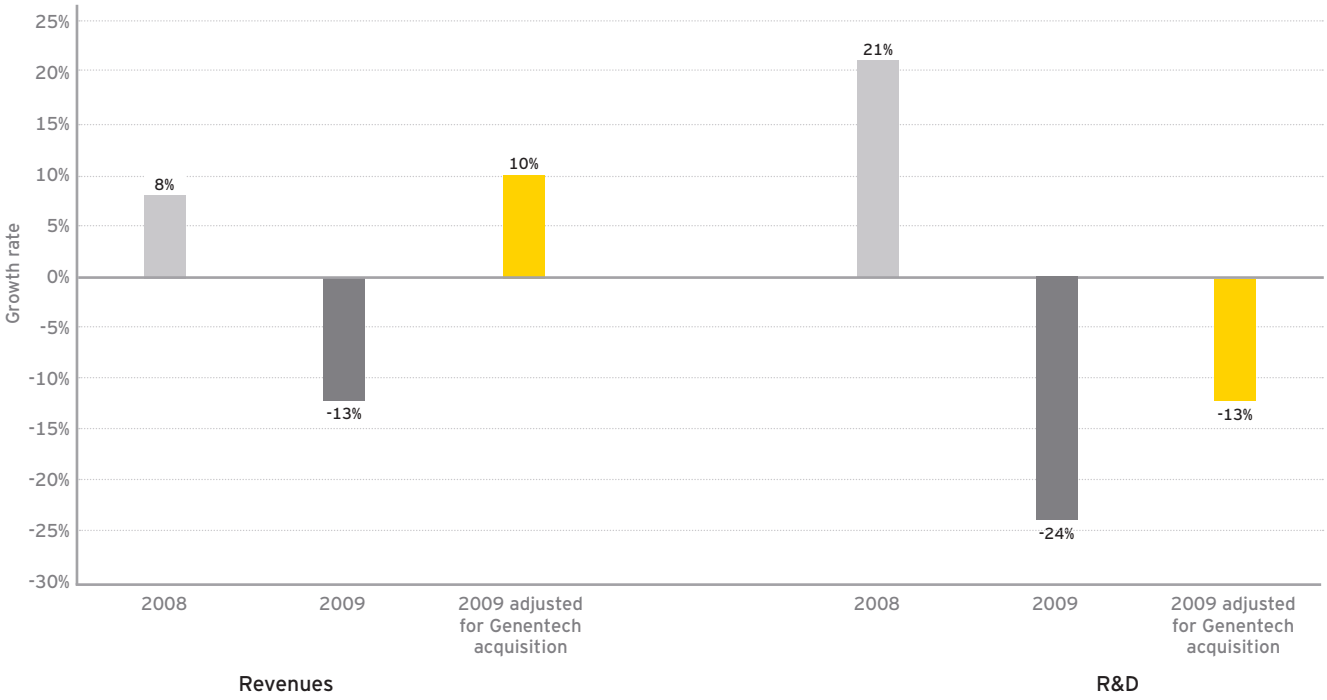
Ernst & Young survival index, 2008–09

	US		Europe		Canada	
	2009	2008	2009	2008	2009	2008
More than 5 years of cash	30%	20%	45%	28%	22%	19%
3–5 years of cash	8%	5%	11%	7%	5%	4%
2–3 years of cash	8%	11%	7%	13%	5%	0%
1–2 years of cash	18%	20%	12%	14%	17%	19%
Less than 1 year of cash	36%	44%	25%	37%	51%	57%

Source: Ernst & Young and company financial statement data
Chart shows share of public companies in each location. Numbers may appear inconsistent because of rounding.

The cost cutting helped boost the sector's net income by a remarkable 68%, as combined net loss fell from €913 million in 2008 to only €288 million in 2009. Out of this €625 million improvement on the bottom line, €147 million came from the decrease in public company count, since most of the companies that ceased operations or were acquired during the year were in a net loss position. Despite slowing revenue growth, Shire was able to deliver strong growth on the bottom line, and a number of other companies – including Genmab, Meda, Photomed, Q-Med and QIAGEN – posted strong increases in net income.

Behind the numbers: the impact of the Genentech acquisition on US biotech financial results



Source: Ernst & Young
Chart shows year-on-year change in aggregate financial results of US publicly traded biotech companies.

Canada

In Canada, the number of public companies declined significantly, from 72 companies in 2008 to 64 companies in 2009 – an 11% reduction. A number of firms were acquired or went out of business in the current downturn, and there was a complete lack of IPOs to replenish the stock. On the private company side, the number of firms declined 9%, from 286 in 2008 to 260 in 2009.

The revenues of publicly traded biotech companies in Canada grew by 9% over the prior year. While this may appear to be better than the 9% *decline* seen a year earlier, the revenue drop in 2008 was actually driven by the acquisition of four large Canadian companies by foreign firms. Normalizing for those acquisitions, the growth rate in Canada for 2008 was actually 26% – significantly higher than the acquisition-adjusted growth rate in 2009, which is 11%.

As in the US and Europe, public companies in Canada have had to engage in significant cost cutting to survive. These efforts have delivered results on the bottom line, where the publicly traded industry's net loss fell an astounding 94%, from US$1.2 billion in 2008 to only US$70 million in 2009 – the industry's lowest overall net loss in the last decade. This improvement on the bottom line had three distinct drivers. First, companies have cut back their expenditures in the current financial climate. Second, a number of loss-making companies have been acquired or ceased operations. Third, significant write-offs of intangible assets over the last few years have abated as very few companies now carry any sizable intangible assets on their balance sheets.

Unfortunately, much of the cost cutting has come at the expense of R&D spending, which fell 44% in 2009. R&D is the driver of future growth in this sector, and this sharp decline could have long-term repercussions for the Canadian industry.

Despite the cost-cutting measures, there was no appreciable improvement in the industry's survival index. While the amount of capital raised by Canadian firms rose significantly during the year, the vast majority of these funds went to a small group of companies, leaving 57% of companies with less than one year of cash on hand.

Boosted by an overall stock market recovery, the industry's market cap surged 56% during the year. Even with this recovery, however, the industry only partially made up for the ground it lost in 2008, when the industry lost 61% of its market value.

European biotechnology at a glance, 2008–09 (€m)

	2009	2008	% change
Public company data			
Revenues	11,904	11,010	8%
R&D expense	3,370	3,454	-2%
Net income (loss)	(288)	(913)	-68%
Market capitalization	44,300	33,426	33%
Number of employees	49,120	48,440	1%
Financings			
Capital raised by public companies	2,091	936	123%
Number of IPOs	3	3	0%
Capital raised by private companies	836	1,005	-17%
Number of companies			
Public companies	171	179	-4%
Private companies	1,619	1,640	-1%
Public and private companies	1,790	1,819	-2%

Source: Ernst & Young
Data were generally derived from year-end information (31 December). The 2009 estimates are based on January–September quarterly filings and preliminary annual financial performance data for some companies. The 2008 estimates have been revised for compatability with 2009 data. Numbers may appear inconsistent because of rounding.

Canadian biotechnology at a glance, 2008–09 (US$m)

	2009	2008	% change
Public company data			
Revenues	2,163	1,979	9%
R&D expense	354	626	-44%
Net income (loss)	(70)	(1,148)	-94%
Market capitalization	6,571	4,217	56%
Number of employees	6,930	7,972	-13%
Financings			
Capital raised by public companies	633	271	134%
Number of IPOs	0	0	0%
Capital raised by private companies	100	207	-52%
Number of companies			
Public companies	64	72	-11%
Private companies	260	286	-9%
Public and private companies	324	358	-9%

Source: Ernst & Young
Financial data for 2009 were converted to US$ using an exchange rate of 1.14 (Canadian per US$), except market capitalization, which was converted using an exchange rate of 1.05. Data for 2008 were converted to US$ using an exchange rate of 1.07, except market capitalization, which was converted using an exchange rate of 1.22. Data for 2008 have been restated to reflect full-year results, since estimates in *Beyond borders 2009* included some estimation of fourth quarter results. Numbers may appear inconsistent because of rounding.

Australia

The performance of the Australian biotech industry reflected trends seen in other major biotech clusters as the global financial crisis took its toll. To see the true picture, however, we need to control for two factors. The first of these is the performance of CSL, Australia's largest biotech company, which dwarfs the rest of the industry. Because of the company's sheer size, CSL's results tend to obscure the performance of the rest of the sector. Even as CSL turned in a robust performance in 2009, driven by strong sales of its key products, many smaller biotech companies struggled.

The second factor skewing the numbers in 2009 is the exchange rate between the US dollar and Australian dollar. The Australian dollar declined by about 16% between 30 June 2008 and 30 June 2009 (Australian companies typically have fiscal years ending in June), which dampened the industry's growth when expressed in US dollars.

The revenues of the Australian publicly traded biotech industry grew from US$3.48 billion in 2008 to US$3.72 billion in 2009 – a 7% increase, significantly lower than the 26% growth rate achieved in 2008. However, this number was skewed by fluctuations in the exchange rate and CSL's performance. When measured in Australian dollars, the industry grew by a scorching 28%, beating the growth seen in 2008. After netting out the impact of CSL's strong performance, the revenues of the rest of the industry actually *declined* by 9% in US dollars.

As in the other major markets, there was considerable improvement on the bottom line. The industry's net income grew by 71% to reach US$545 million. While CSL – which boosted its net income by 63% in fiscal year 2009 – accounted for

Australian biotechnology at a glance, 2008–09 (US$m)

Public company data	2009	2008	% change
Revenues	3,721	3,475	7%
R&D expense	417	436	-4%
Net income (loss)	545	319	71%
Number of employees	11,060	10,110	9%
Market capitalization	18,597	21,557	-14%
Total assets	7,082	6,339	12%
Number of public companies	74	83	-11%

Source: Ernst & Young and company financial data

the bulk of this improvement, the rest of the industry held steady. Without CSL, the industry's net loss in US dollars was essentially flat during the year.

The net income story was driven at least in part by companies' cost-cutting efforts in the current economic environment. As in the US, Europe and Canada, this was reflected in R&D expenditures. The industry's R&D spending declined by 4%, from US$436 million in 2008 to US$417 million in 2009. Without CSL (which increased R&D spending by 38% during this period), the industry's R&D expenditures would have declined by a far steeper 22%.

A transformational year

In more ways than one, 2009 has indeed been a transformational year for the biotechnology industry. After years of double-digit increases on the top line, the industry's revenue growth slowed considerably. With a forecasted slow recovery for the global economy and mounting pricing pressure on drugs, the downward pressure on revenues – in the absence of new breakthrough therapeutics – could well be part of the new normal for years to come.

R&D spending will remain an important driver. Biotech remains an innovation-driven business, and R&D is inherently unpredictable. While companies and investors will, and should, continue to look for more efficient ways to develop products in the new normal (see the *Global introduction* article for more details), drastic reductions in R&D spending could result in lower levels of innovation and new product introductions in years ahead – with negative repercussions not just for the industry's performance, but also for its ability to attract investors.

The encouraging news, though – and perhaps the biggest transformation of all – is in the industry's bottom line. Net income was boosted considerably by cost-cutting efforts, which are likely to continue given the more challenging fund-raising environment. Much of the cost cutting in 2009 was precipitated by short-term thinking and the very real need to survive. In many cases, companies may well have overreacted – trimming not just fat, but R&D muscle and bone as well. However, as biotech finds a new equilibrium, we are likely to see a middle ground emerge, where the industry continues to develop groundbreaking innovations but finds more efficient approaches and business models for commercializing products and technologies. That would be good news indeed – not just for biotech companies but for the investors who back them and the patients who need their innovative new products. ▶

Søren Carlsen
Novo Ventures
Managing Partner

Venturing forth with creative approaches

The biotech industry has gone through several funding cycles, ranging from optimism and financial abundance to severe capital scarcity. In 1999 and 2000, many companies were formed with medium-sized financial injections followed by several follow-on rounds with new investors at higher valuations and an IPO as the intended exit. This model ended after the bursting of the genomics bubble. With follow-on venture investors facing "down rounds," the focus shifted to assembling a strong syndicate from the beginning that could support the company for several years. However, this model worked best in the US, where there are more investors with the requisite experience, deep pockets and risk appetite. In Europe, the model has instead largely been one of "drip feeding" companies.

Of course, things have become dramatically more difficult in the last one to two years. In both Europe and North America, VCs are often struggling to participate in follow-on rounds, since it is taking more time and money than originally anticipated to carry a company to a healthy exit, and many funds — including some very respected names — have had trouble raising fresh capital.

In response, biotech companies have lowered their burn rates, sometimes even at the expense of promising R&D projects. Alternatively, companies are trying to partner their assets earlier than originally anticipated. This might seem the best option in a stressed situation, but having investors with financial strength to develop assets often creates much more value for shareholders. Similarly, in exits through acquisition, stressed investor syndicates might be forced to sell companies prematurely at excessively low valuations.

Creative approaches for challenging times

Novo Ventures has a funding structure and financial strength well suited for these challenging times. In an increasingly tight capital environment, we are often using very lean or semi-virtual company operations. For instance, we founded Thiakis with a co-investor in 2006 based on some interesting molecules involved in appetite regulation from London's Imperial College. From the start, the company was run as a focused project with a lean, almost virtual, organization. The idea was to simply find the best molecule in terms of pharmacokinetics, weight loss and side effects. Our plan — to sell the company if it successfully completed Phase IIa trials — was borne out when we sold Thiakis to Wyeth in December 2008. Wherever possible, we are looking for similar approaches in today's market. In a recent case from 2010, we sold the company Novexel to AstraZeneca. In the negotiations, it was a clear advantage that we had the financial muscle to develop the company further ourselves (and Novo Ventures actually bought some shares from co-investors some months before the sale).

In Europe, start-up formation has dwindled due to lack of funding. Many VCs are focused on supporting their existing portfolios, with relatively little for new companies. But patients need improved products more than ever, and there is a lot of exciting university research. So we started the Novo Pre-Seed and Seed programs in 2007. The Pre-Seed program provides managerial and financial support as outright grants, with no claims of ownership or payback requirements. The Novo Seed program is restricted to Nordic companies and operates on commercial terms typical for venture funding. We now have around 10 companies in our seed portfolio. Our goal is to support these start-ups in a lean and focused way, helping them to mature projects and becoming interesting for international VCs.

In today's environment, some investors in syndicates often do not have the financial strength and patience to fully explore the potential of a company's assets. In many cases, we have been investing above our pro rata to keep supporting promising projects, while obviously remaining prudent and focused on costs. In addition, we have created our latest program — Novo Growth Equity — to invest in companies with products in the commercialization stage.

Our funds are set up as evergreen funds. This gives us greater flexibility and patience in today's funding environment, where exits are taking longer. Novo A/S — which operates Novo Ventures, Novo Seeds and Novo Growth Equity on behalf of the Novo Nordisk Foundation — is the majority shareholder in publicly listed Novo Nordisk A/S and Novozymes A/S. The large and ongoing dividend stream from these shareholdings provides the key source of investment capital.

Today, Novo invests up to US$300 million annually in life science companies, making it one of the world's largest biotech funds. In trying times, it is particularly important to focus on the smartest way to use resources, and many of our approaches provide funding options in this difficult financing environment. ▶

Financing

A higher bar

After a dismal performance in 2008, biotech funding levels rebounded nicely in 2009. In the US, Europe and Canada, biotech companies raised US$23.2 billion, a 42% increase relative to 2008. While this was about 20% lower than the levels achieved in the "easy money" era of 2006 and 2007, it is certainly impressive in today's more challenging financing environment. But the real story – a tale of "haves" that raised large sums and "have-nots" that must cross higher hurdles to attain funding – lies in the details behind the totals.

While venture capital totals largely held steady in 2009 (as they had in 2008, even amid the worst of the financial crisis), the stories in the US and Europe could hardly have been more different: the US had its second-best venture funding year in the decade, while Europe had its worst. Across all geographies, new companies seeking venture capital faced a higher bar from investors.

On the other end of the spectrum, there was plenty of capital available for established public companies. Follow-on funding from the public equity markets increased more than 250% to US$6.6 billion – the second-highest total of the decade. In Europe, follow-on funding reached the highest level of the decade. However, a few "haves" dominated the picture, with a handful of very large transactions accounting for the majority of capital raised.

For companies looking to raise public equity for the first time, the picture remained somewhat murky. While a few companies successfully tested the waters in 2009, many others remain cautiously hopeful and are waiting in the IPO queue. The aftermarket performance of IPOs remains mixed, however, which is a barrier to more widespread investor enthusiasm for new issues.

Recovery and the new normal

In last year's *Beyond borders*, we discussed in some detail the impact that the global financial crisis was having on the biotechnology industry. As the biotech industry was swept up in the tsunami that struck the financial markets, many investors – both individual and institutional – sought the safety of higher ground in investments that were perceived to be safe. Others were forced to liquidate because of margin calls as market capitalizations declined in all sectors. As a result, small- and mid-cap biotech companies in particular saw their values decline and their access to capital diminish, in many cases without regard to their underlying fundamentals. Companies took aggressive action to reduce their burn rates and to cast a wide net for financing to stay afloat. In early 2009, the conversation turned to industry consolidation and speculation about how the ranks of companies would shrink over the coming year, either because they were swallowed by acquirers or because they had to cease operations.

As it turns out, despite a significant number of company closings, the industry has been more resilient than many expected. The year started slowly on the fund-raising front, with mature, profitable companies accounting for the majority of funds raised early in the year. By spring, however, there were clear signs of renewed market interest in the industry, catalyzed by several upside clinical surprises in the US, including Dendreon's April release of positive clinical data for its prostate cancer treatment, Provenge. By the end of June, the market caps of small- and mid-cap stocks had increased by 8% and 12%, respectively.

Capital raised in the US, Europe and Canada, 2000–09 (US$m)

	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
IPOs	823	116	2,253	1,872	1,785	2,429	484	602	438	7,312
Follow-ons	6,579	1,840	3,345	6,303	4,600	3,380	4,046	1,070	2,431	15,832
Other	10,044	8,244	16,928	14,930	8,442	11,732	10,174	5,546	4,471	11,676
Venture	5,765	6,131	7,407	5,448	5,425	5,677	4,184	3,578	4,268	5,093
Total	**23,211**	**16,332**	**29,932**	**28,553**	**20,252**	**23,218**	**18,889**	**10,795**	**11,609**	**39,913**

Source: Ernst & Young, BioCentury, BioWorld and VentureSource
Numbers may appear inconsistent because of rounding.

The momentum continued to build in the second half of the year, with a boost from more good news on the clinical trial front, this time from Human Genome Sciences (HGS). In the second six months of the year, capital raised through US follow-on public equity offerings increased more than threefold. However, this financing rebound did not extend to all companies equally. In fact, three companies — HGS, Dendreon and Vertex Pharmaceuticals — accounted for 44% of the more than US$5 billion raised through US follow-on offerings in the second half of the year. In Europe, follow-on fund-raising was even more skewed, with one transaction by QIAGEN accounting for 77% of Europe's follow-on funding for the entire year.

Despite this concentration, increased investor interest in offerings by existing public companies can be an early indicator of the return of the IPO market. Indeed, four IPOs were completed in the US and Europe in the second half, although two were by profitable companies and a third was by a company preparing to launch an approved product. Still, many others started queuing up to test the IPO waters in 2010. As we go to press in April, seven US companies have completed IPOs, while several are in the queue. No European companies have gone public so far in 2010, and only one has filed to do so. The most significant debut was by Ironwood Pharmaceuticals. The company raised about US$215 million at a US$1 billion post-money valuation with significant support from existing investors. In a sign of the times, most companies in the IPO queue are more mature than the typical IPO candidate of four or five years ago. While this presents a challenge for venture investors seeking timely exits, it is a plus for IPO investors seeking less risky investments. As the global financial environment improves, we expect the appetite for IPOs to increase, but we anticipate that the bar placed by investors will remain high.

Public investors are not the only ones raising the bar on their investments. In Europe, venture investing fell 21%, with total venture capital falling to the lowest level of the decade. The year was one of only two years when the industry raised less than €1 billion (US$1.4 billion). For companies that did succeed in raising venture capital, it frequently came at a lower valuation than the previous funding round.

There were a number of causes for this decline in venture investing. Profitable exits, either via the public market or through acquisition, remain challenging, and VCs understand that they will have to reserve more capital to fund their existing portfolio companies longer. As a result, investors are being more and more selective in the types of technologies and therapies they are willing to back, favoring those that are most likely to interest a big pharma or big biotech buyer within a reasonable period of time. In addition, while some prominent firms such as NEA, Index Ventures and Domain, were able to close significant new funds in 2009, the National Venture Capital Association reports that overall inflows into the US venture capital industry declined by 47% in 2009 to the lowest level since 2003. A similar phenomenon occurred in Europe, with some specialized life sciences funds seeking liquidity in their existing portfolio investments in order to demonstrate the returns necessary to raise new capital. While some of the lower capital inflows were the result of firms choosing to stay on the sidelines in a difficult year, 2010 promises to continue to present a challenging fund-raising environment, with the net result being fewer venture funds and lower amounts of investable capital across the industry.

These challenges are driving changes in the biotech investment model itself. VCs are experimenting with new investment strategies, including funding projects to important value-inflection points for eventual sale to a larger company, rather than building stand-alone companies with the attendant infrastructure. As a result, we may see a continued decline in total capital invested, but perhaps not in the number of products under development. Companies are still likely to be built around innovative platform technologies, whereas product stories with more binary outcomes will increasingly fall under these new models. And where will all these product candidates come from? In large part from

the pharmaceutical industry, as pharma companies are forced to rationalize R&D budgets and make tough decisions about their pipeline assets. Pharmaceutical companies – which have historically not done much out-licensing – will increasingly seek to out-license portions of their pipelines, or develop products using risk-sharing structures. (For more discussion of these trends, see this year's *Global introduction* article.)

Even as public investors and VCs are raising the bar, there is broad recognition that a healthy emerging biotech sector is good for innovation and for the overall drug development ecosystem. As pharmaceutical companies access more and more of their drug candidates externally, they will need a vibrant community of innovative companies to take on the risk of early development. In last year's *Beyond borders*, we highlighted one example of pharmaceutical companies cooperating to fund new enabling technologies through Enlight Biosciences. We expect to see other examples of "pre-competitive collaboration," but 2009 was marked more by the increasing prominence of corporate venture capital from several perspectives. In the past, corporate venture capital arms often invested as part of a broader collaboration arrangement or as a smaller player in a VC syndicate. It was also relatively uncommon to see more than one corporate investor in a particular transaction. In 2009, this changed markedly – a prominent example being Aileron Therapeutics, which raised US$40 million in a round in which the venture arms of GlaxoSmithKline, Eli Lilly, Novartis and Roche all participated. In Europe, the importance of corporate venture capital was even more stark, with 8 of the top 10 venture rounds having a corporate investor. Over these eight transactions, Novartis was an investor in six, including Opsana Therapeutics, where they invested alongside the Roche Venture Fund.

Also prominent on the scene in 2009 was the Novartis Option Fund, which closed investment transactions with the likes of Avila Therapeutics, Elixir Pharmaceuticals, Forma Therapeutics, Heptares and Viamet Pharmaceuticals. In these deals, the Option Fund typically purchases an equity interest and obtains the right to license a particular program. Finally, in what may be the start of a trend, Eli Lilly announced it would spin out Lilly Ventures as an independent firm (with US$200 million) so that the venture arm could attract and retain partners who would otherwise not want to be bound by corporate compensation policies, and so that the partners would have the same profit interest as other syndicate investors.

United States

Public companies

At first blush, the rebound in financing for public companies in 2009 was remarkable, especially when layered against the backdrop of the gloom-and-doom predictions that existed at the beginning of the year. Total financing of public companies – including IPOs, follow-on public offerings, private investments in public equity (PIPEs) and debt deals – rebounded to an impressive US$13.5 billion from the anemic US$8.6 billion of 2008. However, as described in this year's *Global introduction* article, the overall biotech funding story continues to be that the money raised is largely funding a very small cohort of companies. In 2009, two-thirds of the total was raised by just 19 companies – which is actually an improvement over 2008, when the same number of companies accounted for 75% of the (significantly smaller) fund-raising total. Despite the fact that the market's appetite for follow-on offerings and PIPEs improved in the second half of 2009, the reality was that the companies raising the five highest amounts of capital accounted for between 44% (in the third quarter) and 78% (first quarter) of total funds raised in each quarter of 2009.

US yearly biotechnology financings, 1998–2009 (US$m)

	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998
IPOs	697	6	1,238	944	626	1,618	448	456	208	4,997	685	260
Follow-ons	5,165	1,715	2,494	5,114	3,952	2,846	2,825	838	1,695	14,964	3,680	500
Other	7,617	6,832	12,195	10,953	6,788	8,964	8,306	5,242	3,635	9,987	2,969	787
Venture	4,556	4,445	5,464	3,302	3,328	3,551	2,826	2,164	2,392	2,773	1,435	1,219
Total	**18,034**	**12,998**	**21,391**	**20,313**	**14,694**	**16,979**	**14,405**	**8,699**	**7,930**	**32,722**	**8,769**	**2,766**

Source: Ernst & Young, BioCentury, BioWorld and VentureSource
Numbers may appear inconsistent because of rounding.

Mature, profitable companies were a big part of this story, with Amgen closing a US$2 billion debt transaction in the first quarter and others following suit later in the year – including Talecris Biotherapeutics (which raised US$600 million), Cephalon (US$500 million) and Bio-Rad Laboratories (US$300 million). Companies with exciting late-stage clinical news also tapped the equity and debt markets to raise significant sums – these included Vertex Pharmaceuticals (US$940 million), Human Genome Sciences (US$851 million), Dendreon (US$601 million) and Incyte (US$540 million).

Vertex has always had a knack for raising money opportunistically and at times creatively, including through the sale of future royalty streams, and this trend continued in 2009. Included in the total above was approximately US$120 million raised through notes secured by certain future milestones payments under the company's collaboration with Janssen related to telaprevir in Europe. The company raised an additional US$35 million through the sale of other milestones in the Janssen agreement and received US$105 million through the modification of an existing collaboration with Mitsubishi Tanabe, bringing Vertex's total fund-raising in 2009 to more than US$1.1 billion.

Companies with earlier-stage technologies or those still waiting for their first clinical breakthrough continued, when possible, to take advantage of market conditions to secure funds utilizing a variety of transactions, including follow-on public offerings, PIPEs, committed equity financing facilities and debt transactions, as well as corporate alliances. What remains sobering, however, is the amount of money required to become a self-sustaining biotech company. In prior editions of *Beyond borders*, we noted that the journey from start-up to sustainability takes US$1 billion to US$2 billion. It is noteworthy that two of the fund-raising stars of 2009, Vertex and HGS, have each raised in excess of US$3 billion and have not yet launched the products that they hope will get them to sustainability. While a fortunate few are sure to emerge every year, the average company must think creatively about its business and financing model to bridge difficult funding periods.

The US IPO drought came to an end in August 2009 with the Cumberland Pharmaceuticals transaction. Cumberland, which raised US$79 million, is a specialty pharma company that acquires late-stage development assets or approved products which it markets to targeted physician populations. The company was founded in 1999 and has been profitable for the last six years. Remarkably, the company raised only US$14 million of equity capital prior to its IPO – in other words, not a typical performance for a biotech IPO candidate, but a welcome development nonetheless.

The Talecris Biotherapeutics IPO, which closed in early October, was even more atypical. The company issued US$550 million of common stock, and Talecris' private equity backers sold shares worth an additional US$400 million. (For more discussion, refer to "Anatomy of a private equity IPO" on the next page.) Talecris, which markets plasma-derived protein therapeutics and operates a network of plasma collection centers, spun out of Bayer Corporation in 2005 and is the successor to entities that trace their history back to Cutter Laboratories, founded in the 1940s.

Quarterly breakdown of Americas biotechnology financings, 2009 (US$m)

	First quarter 2009		Second quarter 2009		Third quarter 2009		Fourth quarter 2009		Total	
	US	Canada	US	Canada	US	Canada	US	Canada	US	Canada
IPO	$0	$0	$0	$0	$629	$0	$68	$0	$697	$0
	(0)	(0)	(0)	(0)	(2)	(0)	(1)	(0)	(3)	(0)
Follow-on	$538	$0	$698	$77	$1,800	$37	$2,129	$24	$5,165	$138
	(5)	(0)	(8)	(4)	(22)	(4)	(19)	(2)	(54)	(10)
Venture	$1,152	$24	$992	$31	$1,079	$26	$1,333	$19	$4,556	$100
	(96)	(6)	(71)	(10)	(99)	(11)	(86)	(9)	(352)	(36)
Other	$2,797	$35	$2,102	$402	$1,621	$30	$1,096	$29	$7,617	$495
	(49)	(5)	(90)	(11)	(91)	(7)	(63)	(5)	(293)	(28)
Total	**$4,488**	**$58**	**$3,792**	**$510**	**$5,129**	**$93**	**$4,626**	**$71**	**$18,034**	**$733**
	(150)	**(11)**	**(169)**	**(25)**	**(214)**	**(22)**	**(169)**	**(16)**	**(702)**	**(74)**

Source: Ernst & Young, BioCentury, BioWorld, Windhover and VentureSource
Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.

The final 2009 IPO to close in the US was Omeros, which raised US$68 million in another early-October transaction. Unlike the two transactions discussed above, Seattle-based Omeros fits the mold of most biotech IPOs. The company's most advanced product candidate, based on its PharmacoSurgery platform, is in Phase III trials.

While Talecris saw its stock price increase from the date of the transaction through year-end, both Cumberland and Omeros demonstrated the risk that investors in small-cap stocks take. The stocks lost 19% and 30% of their IPO values by the end of 2009, respectively.

Venture capital

The trend of a small number of companies comprising a significant portion of total capital raised extended to venture-backed companies. In 2009, only 45 companies accounted for fully half of total venture capital raised by US companies. This total was led by the remarkable US$146 million raised by Boulder, Colorado-based Clovis Oncology. Clovis was founded by former executives of Pharmion, which was sold

A closer look

Michael Constantino
Ernst & Young LLP

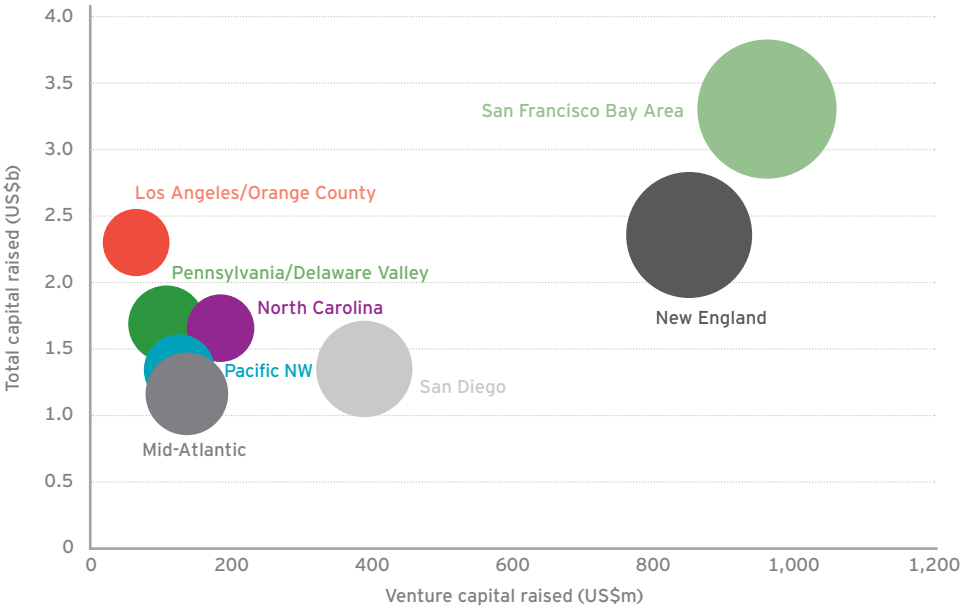
Anatomy of a private equity IPO

The largest IPO of 2009 was not a traditional transaction by biotech standards — both because of the size of the company and because of the size of the transaction. The IPO raised US$1.1 billion, including US$550 million of new money for the company, and provided a very healthy return for investors.

North Carolina-based Talecris Biotherapeutics, which was carved out of Bayer in 2005, now has 5,000 employees and posted 2009 revenues of US$1.5 billion and a net income of US$154 million from the sale of plasma-derived protein therapeutics. The company's legacy extends back many decades through several acquisitions, culminating with the purchase from Bayer by private equity firms Cerberus Capital Management and Ampersand Ventures for US$450 million — of which the investors contributed US$125 million and the rest was funded via Talecris debt and equity issuances. Ampersand also contributed a plasma business it had previously purchased. Following the carve-out, the company undertook a rapid vertical integration of its blood plasma supply chain to solidify its primary source of raw materials. At the end of December 2009, this consisted of 69 blood plasma centers. In 2006 and 2007, management and the board also focused on positioning the company for new product introductions and global expansion through investment in systems, R&D and the addition of a substantial number of new employees.

On the financing side, in 2007, the firm's PE backers executed a recapitalization transaction whereby Talecris borrowed in excess of US$1 billion and paid its investors a dividend of approximately US$800 million — already a sizeable return on the initial investment. In 2008, the company prepared for an IPO, but instead accepted a US$3.1 billion takeover offer from CSL Ltd., itself a significant global player in blood fractionation derived products. The acquisition was ultimately not culminated because of anti-trust issues raised by the US Department of Justice. As a result, in 2009, Talecris jumped back into the IPO fray, debuting as a public company in an October 2009 transaction in which the company and its investors sold an aggregate of 56 million shares at US$19 per share. Following the transaction, the company's market capitalization was US$2.3 billion; the PE investors had received aggregate proceeds from dividends, sales of stock and other fees in excess of US$1.3 billion; and the investors still controlled approximately 50% of Talecris' common stock — an incredibly successful outcome both for the business and its investors.

Capital raised by leading US regions, 2009



Source: Ernst & Young, BioCentury and VentureSource
Size of bubbles shows number of financings per region

to Celgene in 2008 for US$2.9 billion. Clearly the top-tier investor group in Clovis hopes this team can create similar value. In addition to Clovis, there were seven other first-round financings in excess of US$30 million, most located in the traditional start-up hotbeds of Northern California, San Diego and the Boston area. This included Flexion Therapeutics, which raised US$42 million. (For more information on Flexion's activities and approach, see "Lean proof of concept" by Michael Clayman, the company's CEO).

The largest round raised by an established company was the US$71 million raised by Zogenix in two tranches. Zogenix is a specialty pharma company focused on pain and CNS disorders, and it had originally filed to go public in 2008 but withdrew that offering given the difficult funding environment. Other significant venture financings included the US$88 million raised in two rounds by Xanodyne, another specialty pharma company focused on pain management and women's health, and the US$70 million raised by BioVex, a developer of vaccines for the treatment of cancer and infectious disease. Developers of so-called third-generation sequencing technologies Pacific Biosciences and Complete Genomics raised US$68 million and US$45 million, respectively.

Geographic distribution

San Francisco Bay Area and New England once again outpaced all areas in terms of total fund-raising in 2009, garnering US$3.3 billion and US$2.4 billion, respectively. In terms of venture capital, the two regions are virtually equal, with New England having a slight lead in number of venture rounds and Northern California having the advantage in capital raised. The Los Angeles area ranks as the third-largest region, but almost entirely because of a single transaction by Amgen. North Carolina saw its total increase as a result of the IPO and subsequent debt offering completed by Talecris. Likewise, the Pennsylvania/Delaware Valley region saw its total ascend on the back of big financing years from Cephalon and Incyte.

Europe

Public companies

While total fund-raising by publicly traded European biotechs more than doubled compared to the lows seen in 2008, it is once again, a story of the haves and the have-nots. A significant majority of the increase in 2009 can be attributed to two transactions: a €461 million (US$643 million) follow-on offering by Netherlands-headquartered QIAGEN, and a €449 million (US$626 million) debt transaction by Ireland-based Elan. These two transactions accounted for 44% of all funds raised by public biotechs in Europe in 2009. In 2008, the top five fund-raisers accounted for a similar percentage of the total capital raised, with the largest transaction being a €157 million (US$231 million) rights offering by the Swedish company Meda. Absent QIAGEN and Elan, fund-raising by public companies would have increased by 26%, which is still respectable but must be considered in light of the overall 78% decline that occurred in 2008 as compared to 2007. Other notable follow-on offerings in 2009 included NicOx of France (€70 million, US$98 million), NeuroSearch of Denmark (€58 million, US$81 million), UK-based Proximagen (€56 million, US$78 million) and Sweden-based Biovitrum (€52 million, US$73 million).

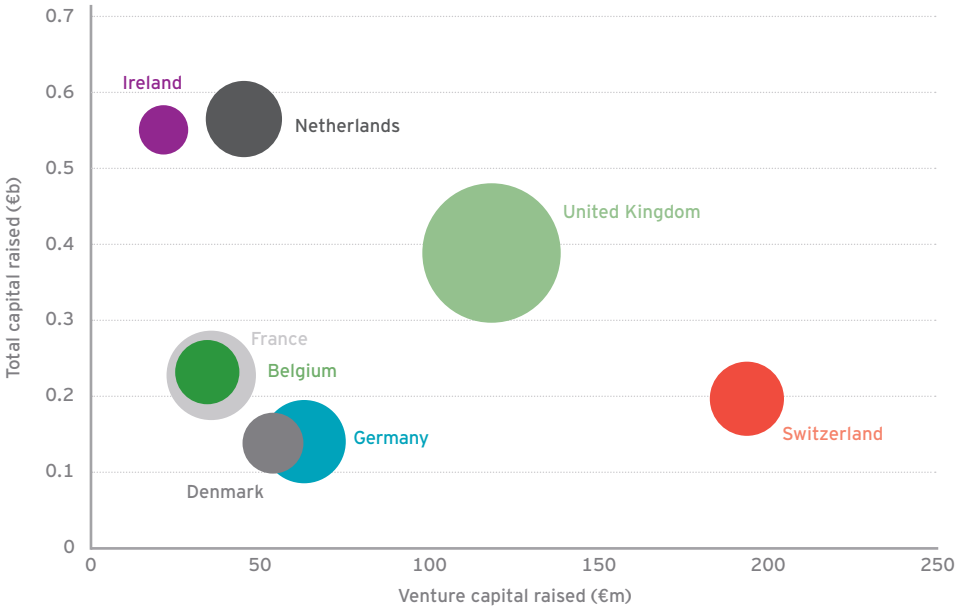
The IPO market in Europe remains largely closed. Unlike the US, where several companies entered the IPO queue at the end of 2009, European companies and investors have been more cautious, although there is an expectation that we may see movement in the second half of 2010. The only institutional-sized IPO transaction in 2009 was Movetis, which raised €98 million (US$137 million) in December – the third-largest financing of the year in Europe. Movetis is a Belgium-based specialty pharma company which spun out of Johnson & Johnson in 2006 and is focused on gastrointestinal diseases. Its lead product, Resolor, was approved for marketing by European authorities in October and was launched in January. Switzerland-based mondoBIOTECH completed a listing on the Swiss Exchange in August, raising no new capital. The company subsequently completed a small rights offering in early 2010. mondoBIOTECH, which also expanded its information technology operations in Silicon Valley in 2009, is focused on using IT and data management to discover therapies for rare diseases based on known peptides and other substances.

Quarterly breakdown of European biotechnology financings, 2009 (€m)

	First quarter 2009	Second quarter 2009	Third quarter 2009	Fourth quarter 2009	Total
IPO	€0	€0	€5	€98	€103
	(0)	(0)	(2)	(1)	(3)
Follow-on	€3	€54	€465	€76	€597
	(2)	(3)	(4)	(6)	(15)
Venture	€253	€139	€88	€311	€790
	(42)	(34)	(30)	(45)	(151)
Other	€147	€175	€569	€499	€1,390
	(32)	(40)	(34)	(37)	(143)
Total	€403	€367	€1,127	€983	€2,881
	(76)	(77)	(70)	(89)	(312)

Source: Ernst & Young, BioCentury, BioWorld, Windhover and VentureSource
Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.

Capital raised by leading European countries, 2009

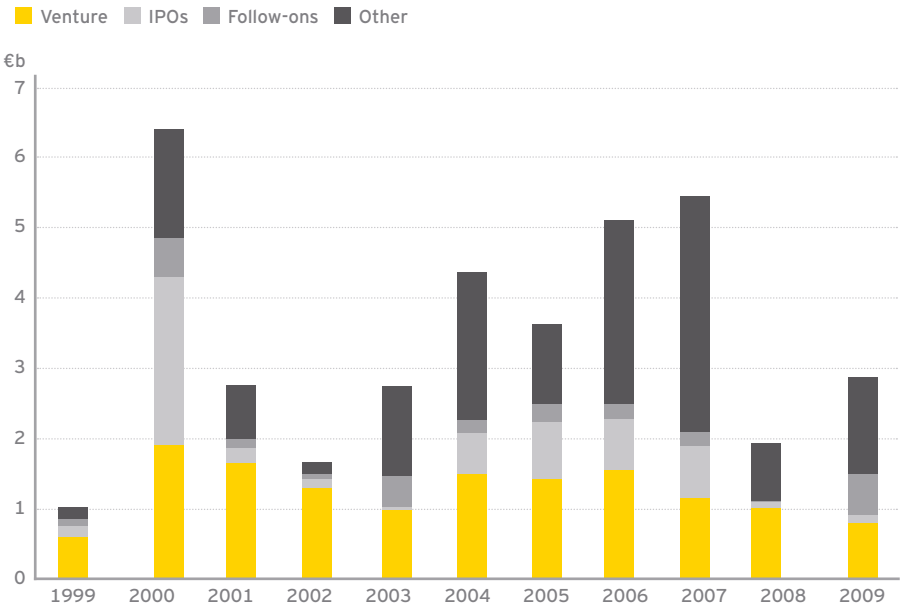


Source: Ernst & Young, BioCentury and VentureSource
Size of bubbles shows number of financings per country.

Venture capital

There were 19 transactions of at least €15 million (US$20.9 million) in 2009, which comprised 55% of total venture capital raised. Importantly, unlike the US, none of these were first-round financings. In fact, there were only two first-round financings in excess of €10 million (US$14 million): Rotterdam-based arGEN-X, which raised €12.5 million (US$17.4 million) for the development of its human antibody platform, and Milan-based Ethical Oncology Science (EOS), which raised €12.2 million (US$17 million). EOS' lead product candidate is a dual VEGF/FGF inhibitor that is in Phase I development. In aggregate, first rounds represented 34% of total transactions, indicating a relatively strong start-up picture, but these deals only accounted for 14% of total funds raised. In contrast, 22% of venture rounds in the US were first-round financings; however, these transactions accounted for 21% of total venture capital investments (18% if the outsized Clovis Oncology transaction noted

European yearly biotech financings, 1999–2009



Source: Ernst & Young, BioCentury, BioWorld, VentureSource, Windhover and company news via NewsAnalyzer

above is excluded). Thus, while the pace of start-up activity is robust in Europe, these companies start life with far less capital than their US counterparts. This clearly puts a premium on capital-efficient R&D strategies, but it also suggests the possibility of a lower bar around company formation in Europe, with investors preferring to mete out capital in much smaller amounts.

The largest venture round in Europe was the €41 million (US$57 million) raised by Geneva-based NovImmune, which is developing therapeutic monoclonal antibodies. The round included an investment by Novartis Ventures. Germany's Probiodrug raised €36 million (US$50 million) to continue its development of products to address neurodegenerative and inflammatory diseases, including Alzheimer's. Other significant rounds included Denmark's Symphogen (€33 million, US$46 million), Switzerland's Molecular Partners (€30 million, US$42.5 million) and Evolva (€29 million, US$40.4 million), and Spain's Cellerix (€27 million, US$37.6 million). Evolva subsequently completed a reverse merger with Arpida, Ltd., and listed its shares on the Swiss Exchange.

Geographic distribution

While Europe is a "common market," with investments regularly flowing across borders, it is interesting to note that the 21% decrease in venture capital investing did not hit all countries equally. Switzerland actually achieved a 57% *increase* in venture capital investment, whereas France (down 49%), Germany (down 60%), the Netherlands (down 49%) and the United Kingdom (down 17%) all suffered significant declines. Amazingly, if one excludes Probiodrug's financing, German biotechs raised only about €42.6 million (US$59.4 million) in all of 2009.

Overall, the Netherlands and Ireland led in total financings because of the previously mentioned QIAGEN and Elan transactions (while QIAGEN has its headquarters in the Netherlands, substantial operations are in Germany). The UK led in the total number of rounds and was third in overall financings, trailing only Switzerland in venture capital raised.

Canada

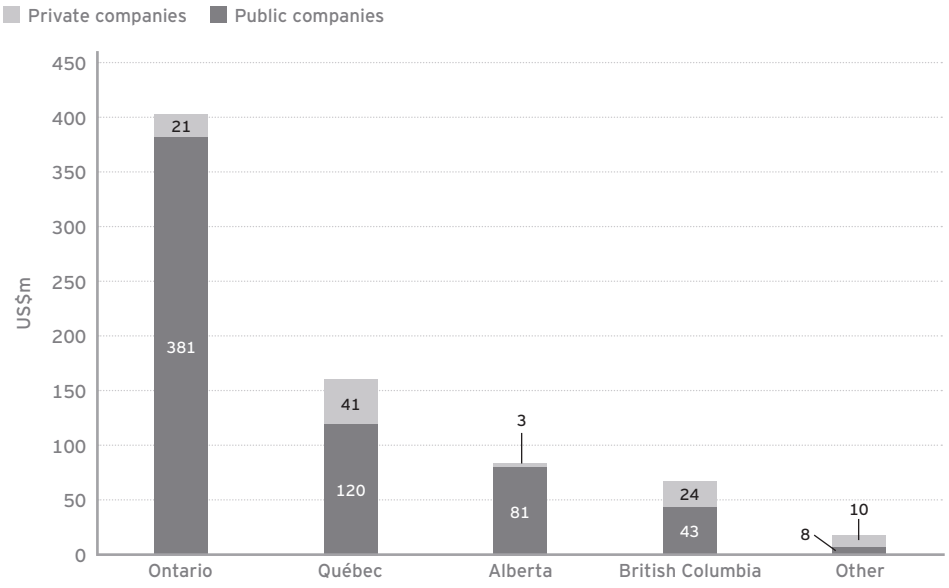
In 2009, the Canadian biotechnology industry raised slightly more than US$733 million, an increase of US$255 million compared to 2008. Public companies raised about US$633 million, a US$362 million increase over 2008. However, this money went to a relatively small set of companies, with one transaction – the US$325 million debentures issue by Biovail – accounting for 44% of the total amount raised by the

Canadian yearly biotechnology financings, 2000–09 (US$m)

	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
IPOs	0	0	5	9	160	85	0	10	42	103
Follow-ons	138	80	580	925	295	296	723	186	621	364
Other	495	191	122	664	242	139	416	132	155	258
Venture	100	207	353	205	313	271	206	199	388	546
Total	**733**	**478**	**1,060**	**1,803**	**1,010**	**791**	**1,345**	**527**	**1,206**	**1,271**

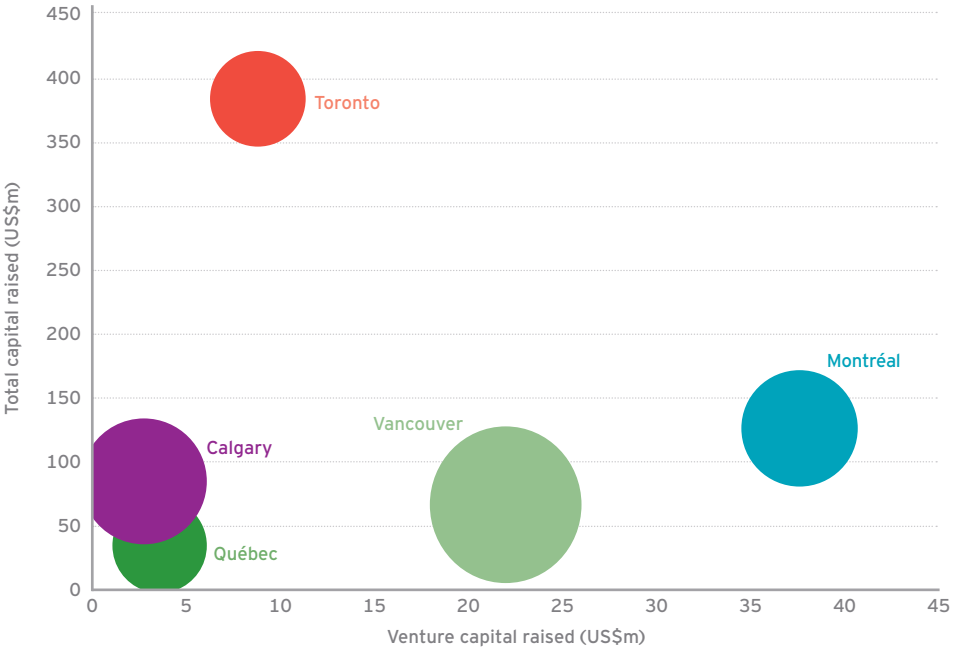
Source: Ernst & Young, Canadian Biotech News *and company websites*
Numbers may appear inconsistent because of rounding.

Capital raised by Canadian province, 2009



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

Capital raised by leading Canadian biotech clusters, 2009



Source: Ernst & Young, Canadian Biotech News *and company websites*
Size of bubbles shows number of financings per region.

industry. In the absence of this transaction, the year's total would have been only US$408 million – the lowest level in the last decade.

For the second year in a row, there were no IPOs, though Halifax-based ImmunoVaccine Technologies went public through a reverse takeover and concurrently raised about US$7.8 million. Follow-on public offerings amounted to US$138 million in 2009, compared to US$80 million in 2008. This increase can primarily be attributed to Paladin Labs' secondary offering of US$50 million; none of the other follow-ons exceeded US$20 million.

There was a sharp decline in venture capital in 2009, a major source of concern for the Canadian industry's long-term prospects. Venture funding decreased from US$207 million in 2008 to US$100 million in 2009 – by far the lowest level seen in the last decade. One company – Montreal-based Enobia – received 16% of this total. Ontario, in particular, saw a very significant decline in venture funding, from US$109 million in 2008 to US$21 million in 2009.

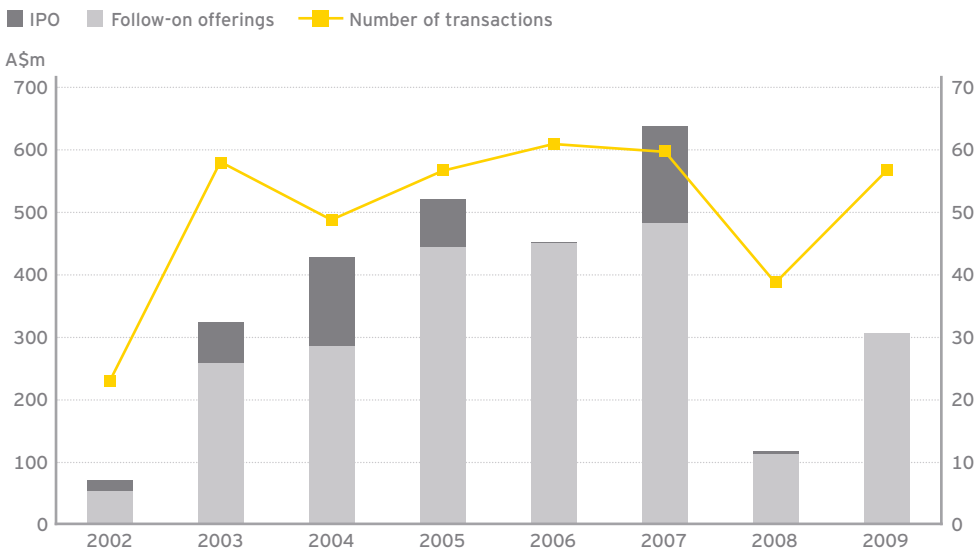
The credit crisis has impacted biotechnology companies harder than firms in most other sectors. Facing bleak capital markets, several Canadian biotech firms turned to non-traditional sources of capital. Government funding – primarily for plant construction and research projects but excluding research grants – generated more than US$11 million in 2009, or about three times the amount raised in 2008. Another significant funding source for public companies was the sale of tax losses, which accounted for US$22 million. Many public companies compensated for the funding shortfall by turning to some interesting research collaborations.

The provincial distribution of funding remains similar to that in previous years.

Ontario-based firms raised over US$400 million, more than any other province (due principally to the Biovail financing discussed above), followed by Quebec firms, which raised US$161 million. In a surprising show of strength, Alberta companies raised US$84 million, while British Columbia's firms raised US$67 million.

There was a similar surprise in the cross-city analysis of capital raised. While Montreal, Vancouver and Toronto continued to lead the pack, companies in Calgary raised US$84 million, third only to Montreal and Toronto. The increase in funding from Calgary can be attributed to Oncothyreon and ResVerlogix, which were both very active in 2009 and accounted for 56% of the funding in Calgary.

Australian biotech public equity raised, 2002–09



Source: Ernst & Young, Bioshares and company annual reports

Australia

In Australia, the amount of capital raised by publicly traded companies through equity financings rebounded sharply, from A$119 million (US$106 million) in 2008 to A$307 million (US$229 million) in 2009. While this represents an encouraging recovery over the prior year, the amount raised in 2009 is still the second-lowest in any year since 2002 and is about 40% lower than the annual average seen between 2005 and 2007. The capital markets remained closed to biotech companies looking to issue shares for the first time, and there were no IPOs of Australian companies during the year.

As in many markets, the bulk of the money went to a relatively small group of companies. Five firms – Avexa, Bionomics, Pharmaxis, QRxPharma and Starpharma Holdings Limited – accounted for more than half the public equity capital raised during the year. Melbourne-based Avexa led the financing totals for the year, with A$41 million (US$31 million) raised in several different offerings. Following the failed merger with Progen in early 2009, Avexa turned to its shareholders and raised A$17 million (US$12.7 million) in a rights issue followed by an A$11 million (US$8.2 million) private placement and a A$15 million (US$11.2 million) oversubscribed shareholder purchase plan. These funds were utilized to advance the company's apricitabine (ATC) Phase III study in HIV patients. The A$15.6 million (US$11.6 million) raised by Starpharma through a private placement to institutional and sophisticated individual investors is to be used to finance the completion of Phase III clinical trials.

Other markets

For noteworthy financing events in other markets, refer to the *Country profiles* section.

Getting creative

Challenging times have typically inspired creativity in biotech companies, so it is not surprising that companies have shown an increased interest in other sources of capital as the usual funding sources have become increasingly constrained. This has ranged from using asset sales and alliances to raise capital to exploring funding options from disease foundations and government grants. Economic development incentive programs (see *A closer look* on the next page) provide another potential source of capital, as state and local governments – pressures on their own coffers notwithstanding – are often still interested in developing their local biotech clusters.

Looking ahead

The amount of investment capital available for the biotech industry will depend on the pace of economic recovery in the

developed countries — and whether that recovery takes the shape of a "U" (slow) or a "W" (a double-dip downturn). Thus biotech companies — particularly the vast majority that are unable to finance on the heels of breakthrough clinical news — will have to navigate an uncertain and likely volatile fund-raising environment for the foreseeable future. Given the substantially slower pace of fund flows into the venture capital industry, the biotech industry will not see a quick return to the venture funding levels of 2007 and 2008. Venture capitalists, whether surviving or thriving, will continue to raise the bar on the companies they back and will explore alternative models to deploy capital more efficiently.

Still, corporate venture capital — whether direct or funneled through established VC firms — is almost certainly going to increase, as pipeline-starved pharma companies have a vested interest in fostering a drug discovery ecosystem that includes a healthy number of innovative and focused biotech companies. Expect to see new investment and collaboration structures that include increased optionality for investors and companies. ▶

A closer look

Ron Xavier
Ernst & Young LLP

Tapping economic development incentives

As funding options have dwindled in the current financing environment, companies need to be increasingly creative in finding new sources of capital. It is not surprising that state and local economic development incentives are getting increased attention, since such incentives can help improve cash flow, pay for capital acquisitions and job creation, and provide financing at below-market rates.

But the labyrinth of state and local economic development agencies is unfamiliar territory for many biotech companies, which have traditionally focused on conducting R&D and raising money from VCs and the capital markets. To secure a comprehensive incentives package, companies often need to meet with multiple state and local agencies several times, complete lengthy applications and collect extensive documentation — all while trying to keep their projects on track and on time.

To succeed, companies need a strategic approach that incorporates three critical elements:

Effective data collection. Many incentives programs require a company to commit to certain levels of capital investment and/or job growth or retention. Consequently, it is critical to have ready access to meaningful data that can inform incentives-related decisions. This includes projected capital investment data (both routine and extraordinary spending) as well as data on projected human resources needs (job creation, layoffs, consolidations, training and employee-development needs).

A single uniform process. The process of obtaining economic incentives is an ongoing one that requires monitoring over time. The process begins with reviewing the capital and human resource investment data to identify and qualify potential opportunities. Once a company identifies the incentives programs that are most relevant, the next step is to pursue these opportunities with the relevant governmental authorities. Finally, once these incentives are secured, the company will establish protocols to meet compliance requirements on an ongoing basis.

Stakeholders. The incentives process can affect many different functions within a company, including real estate, operations, human resources, tax, finance and government affairs. A single group or business division is unlikely to have adequate information or resources to effectively pursue and secure a comprehensive incentives package. The most successful incentives plans therefore involve a coordinated effort across departmental lines. Input from all affected groups will ensure the company takes a holistic approach to securing incentives that best meets the company's total needs.

We are already seeing increased biotech company interest in economic development incentives. In the "new normal," the trend is likely to continue. Despite their budgetary pressures, state and local governments regard biotech companies as desirable targets and drivers of long-term economic development and job creation. With the right focus and a strategic approach, there is no reason why more biotech companies should not be able to avail themselves of these funds.

Fred Frank
Peter J Solomon Company
Vice Chairman

Turbulent financial markets and the impact on biotech

The biotechnology industry and financial community are inextricably linked, and for good reason. Biotech R&D is exceptionally expensive and time consuming, making it one of the most capital-intensive industries. Since the vast majority of biotech companies have no operating revenues, raising funding is a constant and unrelenting focus of management and boards.

Much has changed since Genentech's remarkable and historic IPO in 1980. On the first day of trading, the Company's shares soared from the US$35 offer price to more than US$80 — an unprecedented performance at the time. A cascade of public biotech offerings soon followed (Cetus, for instance, raised an astonishing US$122 million in 1981), fueled by exuberant coverage in the lay press about the new world of molecular biology. Reporters talked breathlessly about "magic bullets" that would develop new cures for diseases ranging from cancer to diabetes, while new technologies promised to make R&D far quicker and cheaper.

Today, reality reigns supreme, and accessing capital has become far more challenging and expensive for earlier-stage companies. The turmoil in financial markets has taken a toll on biotech firms, but the situation is not completely dire. We need to place the current situation in context and understand how it has affected longer-term capital market trends to understand this impact.

One of the most significant consequences has been the virtual closure of the traditional IPO market for emerging venture-backed companies. This is not solely attributable to today's unreceptive markets for offerings of younger, still-unprofitable companies; rather, it also reflects some longer-term, industry-specific trends. First, the market performance of biotech IPOs in recent years has largely been abysmal. Second, a typical biotech IPO provides only enough capital to extend the R&D "runway," but not enough to bring a company to profitability and self-sustaining cash flow. This has caused many former IPO investors to back away and focus instead on private investments in public companies (PIPEs). These financings are executed in a very short time frame, and at a small-to-moderate discount to the company's share price. PIPEs give firms sufficient capital to propel them to important value-creating milestones — which has often driven significant post-offering market price increases. Investors get "instant gratification," and since success breeds imitation, the PIPE markets have been noticeably robust.

Big pharma's role in providing biotech companies with fresh capital for R&D — and giving venture investors a pathway to liquidity — has been vital. The two sides have a naturally symbiotic relationship: pharma companies have been capital-long and opportunity-short with respect to their internal research programs, while biotech firms have been short of capital but rich with research opportunities.

This will likely continue, not least because of the abundance of important prescription drugs scheduled to go off-patent between 2010 and 2015. But here, too, things have changed in the current market environment. In the early 2000s, big pharma players frequently acquired biotech firms outright. Today, acquisitions are instead most often structured as sequential payments — even though the pharma buyer owns 100% of the company, the deal includes a series of contingent milestone payments. The upfront cash consideration may equate to one-to-two times the investments in the biotech company to date, while milestone payments account for the vast majority of the announced "acquisition price." Such transactions represent a new model of shared risk that we will likely see in most pharma-biotech transactions. While pharma-biotech deals will continue, a mature, balanced relationship is evolving to reflect the comparative strengths of the participants.

In summary, remember the quote from Walt Whitman: "Traveling roads all even and peaceful you learn'd from joys and prosperity only,/But now, ah now, to learn from crises of anguish ..." Let's hope these crises of anguish are sculpting a viable, mutually beneficial accommodation — especially so since the ultimate beneficiaries are patients. ▶

Deals

A new landscape

Given the realities of a restricted fund-raising environment for biotechnology companies, coupled with the continued need for pharmaceuticals companies to fill their pipeline gaps, it was reasonable to expect 2009 to be another strong year on the transactions front. Instead, M&A activity declined significantly, and the year saw only three acquisitions larger than US$1 billion. Mega-mergers (transactions larger than US$10 billion) involving biotech companies were essentially absent, other than the completion of Roche's tender for Genentech, which really began in 2008.

The number of strategic alliances remained relatively flat compared to the last several years, while their total potential value ("biobucks") declined to 2007 levels.

It is important to put what might appear to be relatively lackluster totals in context by pointing out what they are *relative to*. Both 2007 and 2008 were exceptionally strong years from a deals perspective, with the industry reaching all-time highs on several fronts. As such, holding ground on strategic alliances is hardly shabby. And the distribution of M&As has often been inherently lumpy, since these are larger, less frequent transactions, and since buyers often pause to digest their acquisitions after making large purchases. As such, it may well be premature to over-interpret what could prove to be a one-year hiatus in the action.

Mega distractions

While the fundamentals driving transactions haven't changed, some basic realities did — particularly for big pharma (the buy side of most biotech deals). Over the last several years, companies across the pharmaceutical industry have been revising and refining their strategies, and this resulted in several mega-mergers in 2009. The action started in January, when Pfizer announced that it would join forces with Wyeth. This was followed in March by Merck's announcement that it was merging with Schering-Plough and the completion of Roche's tender offer for the minority stake in Genentech. When one adds Novartis' two-step acquisition from Nestlé of a majority interest in Alcon (the second step of which closed in 2010), the total value transferred in just these four transactions exceeded US$200 billion — handily surpassing the combined value of all pharma-biotech acquisitions over the last decade.

The impact of this consolidation on deal-making with the biotech industry extends beyond the use of capital and the additional debt burden carried by some companies. In the short term, despite claims by the mega-merger participants that they remain open for business with biotech, it is clear such large transactions create significant integration challenges that are a major distraction for management. Beyond all the inward-focused politics of who will get what position is the very real need to realize synergies by rationalizing the product portfolio and pipeline. Until the dust settles, it is difficult for business development functions to move aggressively in pursuit of new technologies or to credibly argue that they are the "partner of choice" for a particular asset. Indeed, none of the acquirers in these mega-mergers undertook a significant biotech acquisition in 2009, although, with the exception of Pfizer, they did remain active in strategic alliances.

Selected 2009 M&As

Company	Country	Acquired or merged company	Country	Value (US$m)
Dainippon Sumitomo	Japan	Sepracor	US	2,600
Bristol-Myers Squibb	US	Medarex	US	2,400
Gilead Sciences	US	CV Therapeutics	US	1,400
Johnson & Johnson	US	Cougar Biotechnology	US	970
H. Lundbeck	Denmark	Ovation Pharmaceuticals	US	900
Onyx Pharmaceuticals	US	Proteolix	US	851
Celgene	US	Gloucester Pharmaceuticals	US	640
Endo Pharmaceuticals	US	Indevus Pharmaceuticals	US	637
Novartis	Switzerland	CorThera	US	620
Alcon	Switzerland	ESBATech	Switzerland	589
sanofi-aventis	France	Fovea Pharmaceuticals	France	514
sanofi-aventis	France	BiPar Sciences	US	500

Source: Ernst & Young, Windhover Information, MedTRACK, BioWorld and company news via NewsAnalyzer

Longer term, pharma consolidation inevitably reduces the number of potential acquirers and collaborators. One only has to consider the example of Pfizer — which today is made up of parts of formerly independent companies such as Wyeth, American Home Products, Warner Lambert, Pharmacia, Upjohn and GD Searle — to see how acquisitions have thinned the ranks of big pharma over the last decade. It is also entirely possible that we are not yet done with the mega-merger wave. Some of the remaining players, including those that have not recently undertaken large acquisitions, could well turn to consolidation to acquire the scale needed for absorbing the increasing risk of drug development.

Finally, most of the mega-transactions, and many smaller deals undertaken by the pharmaceutical industry in 2009, were at least partly based on the strategy of diversification — whether by market (e.g., gaining a foothold in emerging markets), market segment (e.g., consumer products, generics and animal health) or technology (e.g., vaccine and biologic capabilities). These companies will also increasingly be executing transactions in the commercial end of the value chain, including with non-traditional entrants. (For more on this trend, refer to Ernst & Young's 2010 pharmaceutical industry report, *Progressions: Pharma 3.0*.) Biotech companies should expect to see more pharma transactions focused on areas other than the product pipeline in the future.

The pharmaceutical industry needs a healthy ecosystem that continues to sustain innovative biotechnology companies and provide adequate returns to the investors who nurture this innovation. Just as investors in early-stage companies are changing their strategies, big pharma companies are also experimenting with new structures to access innovation, increase their "shots on goal" and share risk.

Bridging the alliance GAAP

In 2009, there were nine strategic alliances between pharma and biotech companies with values that could potentially exceed US$1 billion in the unlikely event that all milestones are achieved. In these nine transactions, the pharma partners made up-front license and other payments totaling about US$900 million.

Remarkably, seven of the nine transactions were completed by big pharma companies headquartered in Europe. This may have something to do with accounting standards, since European companies report under International Financial Reporting Standards (IFRS) which permits the capitalization of up-front payments (and, generally, follow-on milestone payments). US-headquartered companies, on the other hand, must expense license payments for products in development when the payments are made — creating an immediate dent in their reported earnings per share at a time when companies are under increasing short-term earnings pressures.

Everything else being equal, the different reporting standards do provide companies reporting under IFRS more flexibility in structuring transactions. This does not mean, of course, that US pharmaceutical

Selected 2009 alliances

Company	Country	Partner	Country	Potential value (US$m)
Novartis	Switzerland	Incyte	US	1,310
AstraZeneca	UK	Targacept	US	1,240
sanofi-aventis	France	Exelixis	US	1,161
AstraZeneca	UK	Nektar Therapeutics	US	1,160
Bristol-Myers Squibb	US	ZymoGenetics	US	1,107
Takeda	Japan	Amylin	US	1,075
Bristol-Myers Squibb	US	Alder Biopharmaceuticals	US	1,049
GlaxoSmithKline	UK	Chroma Therapeutics	UK	1,008
GlaxoSmithKline	UK	Concert Pharmaceuticals	US	1,000
Johnson & Johnson	US	Elan	Ireland	875
Wyeth	US	Santaris Pharma	Denmark	847
Bayer Schering	Germany	Algeta	Norway	779
Astellas	Japan	Medivation	US	765
Amgen	US	Array Biopharma	US	726
GlaxoSmithKline	UK	Prosensa	Netherlands	668

Source: Ernst & Young, Windhover Information, MedTRACK, BioWorld and company news via NewsAnalyzer
Chart shows potential value, including up-front and milestone payments.

companies will not make any large up-front payments. Pfizer's 2008 transaction with Medivation, for example, included a US$225 million up-front payment.

Included among the largest deals in 2009 were two by AstraZeneca. The first was its September transaction with Northern California-based Nektar Therapeutics for two drugs intended to address the side effects associated with certain painkillers (including an up-front payment of US$125 million and development and nearer-term regulatory milestones of US$235 million). The second deal followed in December, and was with North Carolina-based Targacept for a drug candidate targeted at depression (including an up-front payment of US$200 million and development and nearer-term regulatory milestones of US$540 million). One of the milestones in the Targacept transaction is first commercial sale — a reflection of the times. It is no longer enough to prove that a drug is safe and effective; it also must be approved for reimbursement by payors at a reasonable price.

Novartis also got into the large-alliance act when it partnered with Incyte around a Phase III drug for the treatment of myelofibrosis and an earlier-stage cancer compound that included a US$150 million up-front license fee. Importantly, Incyte retains US rights to the drug — an increasingly visible trend that we discussed in last year's *Beyond borders*. As global markets, particularly in emerging countries, increase in importance, pharma partners are often more willing to accept (and pay handsomely for) ex-US rights. This allows the biotech to transition to commercial operations and control top-line revenue in an important market — a key driver of shareholder value.

Novartis made one of the largest up-front license payments of the year when it paid Vanda Pharmaceuticals US$200 million for the US and Canadian rights to the schizophrenia drug Fanapt. This drug has had its own circuitous path through development. It was originally licensed to US-based Titan Pharmaceuticals from Hoechst, the German drug maker that was later merged into Aventis. Titan immediately licensed it out to Novartis. Novartis returned the drug to Titan after an earlier clinical setback, which then licensed it to Vanda. To the surprise of many, the FDA approved the drug in 2009, which resulted in Novartis re-entering the picture for a second time.

Other deals with large up-fronts in 2009 included sanofi-aventis and Exelixis for several cancer drugs (US$140 million); Astellas and Medivation for a drug to treat prostate cancer (US$110 million); and Biogen Idec and Acorda Therapeutics for ex-US rights to Fampridine-SR, which was approved by the FDA in early 2010 to help improve walking in patients with multiple sclerosis (US$110 million). Biogen-Idec was the only US GAAP-reporting company to pay an up-front fee in excess of US$100 million.

Among US pharmas, Bristol-Myers Squibb extended its "string of pearls" strategy (refer to the article by James Cornelius in last year's *Beyond borders* for more details) by completing significant transactions with two Seattle-area biotech companies — ZymoGenetics and Alder Biopharmaceuticals. Both transactions included up-front payments of US$85 million. In the Zymogenetics deal, BMS gets rights to an early-stage drug program for the treatment of hepatitis C, and from Alder, BMS gains rights to a Phase II biologic for the treatment of rheumatoid arthritis.

Johnson & Johnson took a somewhat novel approach to gaining access to products while sparing its income statement from the burden of an up-front license payment. J&J acquired significant stakes in two European biotech companies, Elan and Crucell, obtaining product rights in the process. In the Crucell arrangement, J&J obtained the rights to co-develop Crucell's universal monoclonal antibody for the treatment

and prevention of influenza in exchange for purchasing an 18% interest in the Netherlands-based company for US$443 million. J&J also purchased 18% of Elan, receiving certain rights to Elan's Alzheimer's program. J&J agreed to provide US$500 million of further development funding for the program in addition to what was initially a US$1 billion payment for the equity interest in the Irish company.

However, the deal was almost undone by a side agreement that would have allowed J&J to fund Elan's acquisition of Tysabri rights from Biogen Idec if the Massachusetts-based company was ever subject to a change in control. After Biogen Idec protested in court claiming the side agreement violated its arrangement

A closer look

Michelle Mittelsteadt
Ernst & Young LLP

Valuing milestones

The M&A environment was fraught with challenges in 2009. As the financial crisis unfolded, "valuation gaps" — chasms between the expectations of sellers and the realities of the market — opened up. To bridge these gaps, transactions frequently included contingent consideration such as payments upon the achievement of development or commercial milestones. In the US, a new accounting rule established by the Financial Accounting Standards Board (known as "SFAS 141R") which became effective in 2009 requires such contingent consideration to be valued and accounted for prior to the resolution of the contingency.

Under SFAS 141R, acquirers must estimate the fair value of the contingent consideration at the time of the acquisition. Buyers must also update that fair value every quarter until all contingencies are resolved.

In determining a value for the contingent consideration, one challenging issue is the use of an appropriate discount rate for research stage milestones, which by their nature carry significant risk. Company disclosures have included discount rates ranging from 6% to 26% applied to probability-adjusted payouts for technical milestones. Clearly, there is little consensus about the degree of risk accounted for in the probability adjustment and in the discount rate. It's worth pointing out that there is less risk around a contingent payment than the associated research project because there is less uncertainty around the contingent payment than the ultimate cash flows associated with the project.

The need to monitor and value contingent liabilities after the deal has closed creates additional challenges. There is the burden of updating timing, probabilities and forecasts on a quarterly basis. Any change in fair value flows through the company's income statement. When a research contingency is ultimately resolved, there could be a "loss" (if the research was successful and the contingent milestone liability is trued up to actual and paid) or a "gain" (if the milestone is not achieved and the related contingent liability is reversed). As a result, acquisitive companies will need to predict the "Day 2" impact on the financial statements from the time the deal is contemplated.

One of the biggest changes in the new accounting guidelines is the capitalization rather than expensing of acquired in-process research and development projects (IPR&D). These assets are not amortized to expense until the R&D is completed and technical uncertainty is resolved, at which time the asset is amortized over its remaining useful life. Typically, the asset value is amortized after commercial launch.

Given the new accounting treatment of these assets, there is far more scrutiny on the valuation of these projects, particularly in regard to the unit of account. For example, when a drug candidate is acquired, should the value be calculated on an aggregate basis for all indications for all geographies, or is it more appropriate to value separately each individual indication being pursued in each major regulatory geography? Clearly this becomes important when testing for impairment after the acquisition and when amortizing the asset. Over the first year of adoption, companies are still trying to determine their accounting policies in this matter, but there has been a trend toward consolidation on a global basis for a given indication, given the relative value of the major markets.

Clearly, there are more valuation challenges under the new accounting standards, and acquiring companies must contemplate these challenges earlier in the deal process because the impacts on reported financial results are long-lasting.

with Elan (the judge agreed) the parties renegotiated the deal to remove the side agreement and reduce the equity investment by US$115 million. Biogen Idec didn't like the side agreement in part because it could discourage other potential acquirers.

Sharing the risk

With biotech companies and their investors needing to secure financing or find exits in a challenging environment, the bargaining power in deals swung toward buyers in 2008 and remained there in 2009. With this shift came an increase in various forms of "risk sharing" arrangements that gave biotech companies more risk than they would have assumed in years past.

On the M&A front, risk-sharing manifested itself in the increasing number of transactions that included milestone payments (sometimes referred to as contingent value rights or CVRs). This was most common in takeouts of private companies, including sanofi-aventis' acquisition of BiPar Sciences for up to US$500 million (including US$125 million of milestones), Alcon's acquisition of ESBATech for up to US$589 million (including US$439 million of milestones), and Novartis' acquisition of Cothera for a potential value of US$620 million (including US$500 million of milestones).

Biotech buyers also used the CVR structure commonly during 2009, in part to bridge differences in perceived value. The more significant biotech-biotech deals with CVRs included Onyx Pharmaceuticals' takeout of Proteolix for a potential value of US$851 million (including US$575 million of potential milestones), Celgene's acquisition of Gloucester Pharmaceuticals for a potential value of US$640 million (including US$300 million of milestones) and Cubist Pharmaceuticals' acquisition of Calixa for US$403 million (including US$310 million of milestones). The CVR structure was not limited to private companies either, as both The Medicine Company's acquisition of publicly traded Targanta Therapeutics and Endo Pharmaceuticals' takeout of publicly traded Indevus Pharmaceuticals included such rights. CombinatoRx and NeuroMed of Canada forged a particularly creative contingent transaction. The two parties struck a merger agreement which had shareholders of each company initially holding 50% of the combined entity. However, much of the value of NeuroMed was tied to receiving FDA approval to market Exalgo, a drug for the treatment of chronic pain. The two parties agreed that if Exalgo was approved by a specified date, the ownership percentage would adjust in the favor of NeuroMed's shareholders. This scenario came to pass when the drug was approved by the FDA in March 2010. CombinatoRx issued additional shares to the former NeuroMed shareholders equaling an additional 10% of the combined company. The approval also triggered a US$40 million milestone payment from Covidien, which will market the drug.

While contingent rights serve a valid business purpose, they can create deal and asset valuation issues for the acquirer, both at closing and in subsequent reporting periods. (For more information, see *A closer look* on the previous page.)

Having options

The use of option structures in biotech deals has been around for awhile. In early 2007, for instance, Amgen paid Cytokinetics US$75 million for an option to license a cardiovascular drug candidate (the company exercised the option in 2009 for an additional US$50 million). In the current environment, however, such structures are becoming increasingly common.

In these arrangements, the buyer pays a fee (and in some cases makes an equity investment) in exchange for the right to license a particular product at a later date (e.g., upon successful completion of a clinical trial). The biotech company typically uses the proceeds from the option transaction to further the product's development. Early in the year, Cephalon and privately held Ception announced an option-based acquisition structure under which Cephalon paid US$100 million (a portion of which was returned to Ception's venture capital investors) for an option to acquire the company for an additional US$250 million following the results of a key clinical trial. In early 2010, Cephalon exercised the option. Cephalon also used this structure in a deal with BioAssets, and Novartis employed acquisition options in deals with Proteon and Elixir Pharmaceuticals, each of which has a potential acquisition price in excess of US$500 million.

Of course, option structures are not limited to M&As; they can also be used in licensing transactions involving individual R&D programs. GlaxoSmithKline has been the most prominent user of option structures in such deals; in 2009 alone the company entered transactions that included option rights with Vernalis, Prosensa, Chroma Therapeutics, Supergen, Concert Pharmaceuticals and others. Buyers may end up paying more for a product that achieves the desired clinical outcome and is later licensed through the exercise of the option. However, over a portfolio of deals, they manage the risk of failure by having multiple "shots on goal" and only paying to license products that have successfully reached the desired outcome. When GSK

exercises the option, it typically takes responsibility for further development and commercialization. As noted in the *Financing* article ("A higher bar"), the Novartis Option Fund has also been active with similar arrangements. The Novartis Option Fund is, however, investing as a financial investor first, and normally does not take on option on the biotech company's lead program.

In prior years, we have discussed another type of option arrangement – the structure used by Symphony Capital to strike deals with several biotech firms – as a financing transaction. In these deals, the biotech company contributes assets to a newly formed entity that is funded and controlled by Symphony, but it retains an option to acquire the new entity or individual assets over a defined time period. The success of the Symphony funding model depended in part on a healthy equity market so that the biotechs could access capital to exercise the options at higher valuations than when the structure was put in place. Given the more restrictive fund-raising environment in 2009 and the fact that even positive clinical news didn't always move a company's stock, Symphony renegotiated the option terms of several existing deals in 2009, including those with Alexza Pharmaceuticals, Dynavax and OXiGENE, thus becoming a significant equity holder in these companies.

Tying the knot

Over its 20-year history, the Roche-Genentech alliance was incredibly productive for both parties. We have often wondered why we haven't seen more examples of such deal structures – once referred to as "the 60% solution" in honor of Roche's ownership stake in Genentech – as it allowed Genentech to grow and adapt largely insulated from short-term stock market pressures. In last year's report, we featured an innovative partnership between Purdue Pharmaceuticals (and affiliates) and Infinity Pharmaceuticals that was intended to achieve the same objective – albeit with Purdue holding a minority ownership interest. With a secure source of financing, the transaction allows Infinity to allocate resources to the most promising product candidates, which may not always be the most advanced items in their pipeline.

A 2009 version of this structure can be found in the expansion of an existing alliance between sanofi-aventis and Regeneron which is focused on the development of monoclonal antibodies. Under this arrangement, sanofi-aventis will pay Regeneron US$160 million per year over seven years to conduct research activities. Sanofi-aventis has the option to take over development of the resulting product candidates as they enter clinical trials. The parties share the profits from the resulting drugs, with sanofi-aventis receiving a preferential profit split until reimbursed for half of the clinical development costs of the product. This allows Regeneron to focus on early discovery and preclinical activities and only pay for clinical development of drugs that are approved. Of course, Regeneron can agree to take on clinical development for any drug that sanofi-aventis takes a pass on. Sanofi-aventis is also a 19% shareholder in Regeneron, but its stake cannot exceed 30% without approval from Regeneron. Like the Purdue-Infinity transaction, the deal does not give sanofi-aventis any board seats. (For more on the motivation behind this transaction see "Succeeding together" by Leonard Schleifer, Regeneron's CEO.)

While not all biotech companies will have the technology platform for this type of arrangement, those that do may want to consider the option of "getting engaged" with a larger, patient and strategically aligned partner.

United States

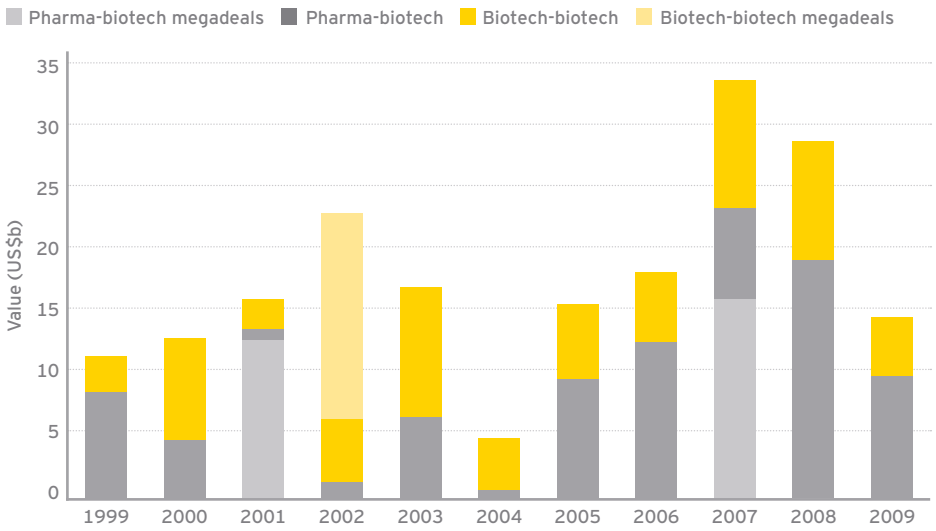
M&As

The saga of Roche's acquisition of the minority interest in Genentech finally came to close in March 2009 when the biotech company's board agreed to a price of US$95 per share, or nearly US$47 billion (more than Merck paid for all of Schering-Plough). This deal closes the book on the most successful and lucrative alliance in the history of the biotech industry. Because of the outsized nature of the deal and the fact that Roche previously controlled a majority of Genentech, we have decided to omit the transaction from the analysis and charts in this article.

Without Roche-Genentech, the value of M&A transactions involving US-based biotech companies decreased by half in 2009 to a total of US$14.1 billion. Only three transactions had a value in excess of US$1 billion. Dainippon Sumitomo Pharmaceuticals of Japan acquired Sepracor for US$2.6 billion, extending the trend of Japanese companies growing their operating footprint in the US through acquisition (see Eisai's acquisition of MGI Pharma in 2007 and Takeda's acquisition of Millennium Pharmaceuticals in 2008). Bristol-Myers Squibb deepened its biotechnology capabilities through the acquisition Mederex for US$2.4 billion. Meanwhile, Gilead Sciences played white knight to CV Therapeutics after Astellas Pharmaceuticals' hostile bid, paying US$1.4 billion to win over shareholders. Astellas is clearly interested in expanding its US presence and in early 2010 returned with another hostile bid – its US$3.5 billion offer for OSI Pharmaceuticals. The next largest acquisition in the US was the US$970 million that Johnson & Johnson paid for Cougar Biotechnology which was developing several oncology drugs, including one in Phase III.

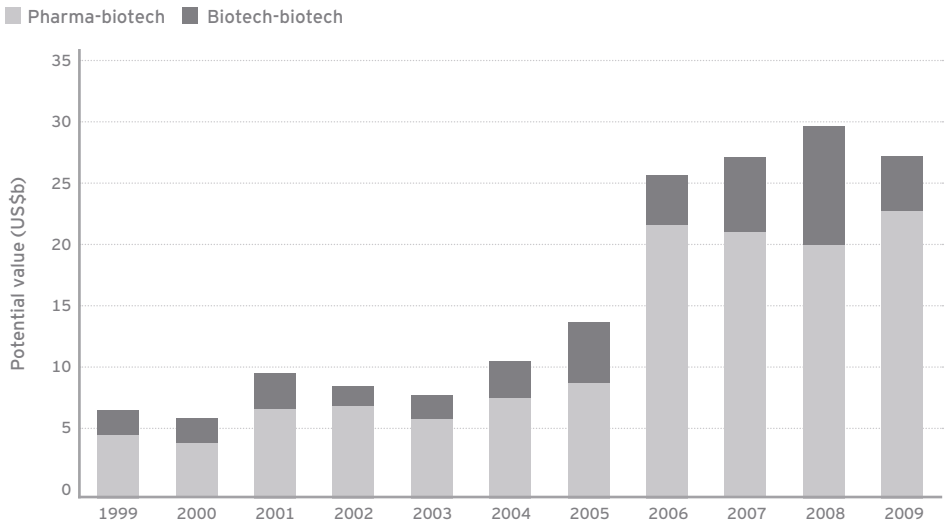
Together, these four transactions comprised 54% of total M&A deal values, including the value of CVRs. In total, there were only 17 acquisitions of US companies in which the value changing hands at closing, exclusive of CVRs, exceeded US$100 million, down from 23 in 2008. These transactions had an aggregate value of US$11 billion, well below 2008's US$29.6 billion.

US M&As, 1999–2009



Source: Ernst & Young, Windhover Information, MedTRACK, BioWorld and company news via NewsAnalyzer
Chart excludes Roche's acquisition of Genentech.

US strategic alliances remain strong



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

Alliances

In 2009, US-based biotech companies entered 132 alliances where financial terms were disclosed (up slightly from 115 deals in 2008). These transactions had an aggregate potential value of US$27.3 billion (similar to the prior year's US$29.6 billion). Of these deals, 97 disclosed up-front payments, comprised of license fees, technology access fees and sales of equity, with a combined value of approximately US$3 billion – essentially unchanged since 2008. The average up-front in 2009 was

US$31 million, down from US$38 million in 2008. We count 21 transactions in 2009 with up-front payments of US$50 million or more, which in aggregate represents approximately two-thirds of the total up-front payment amount – also relatively unchanged compared to 2008.

Europe

M&As

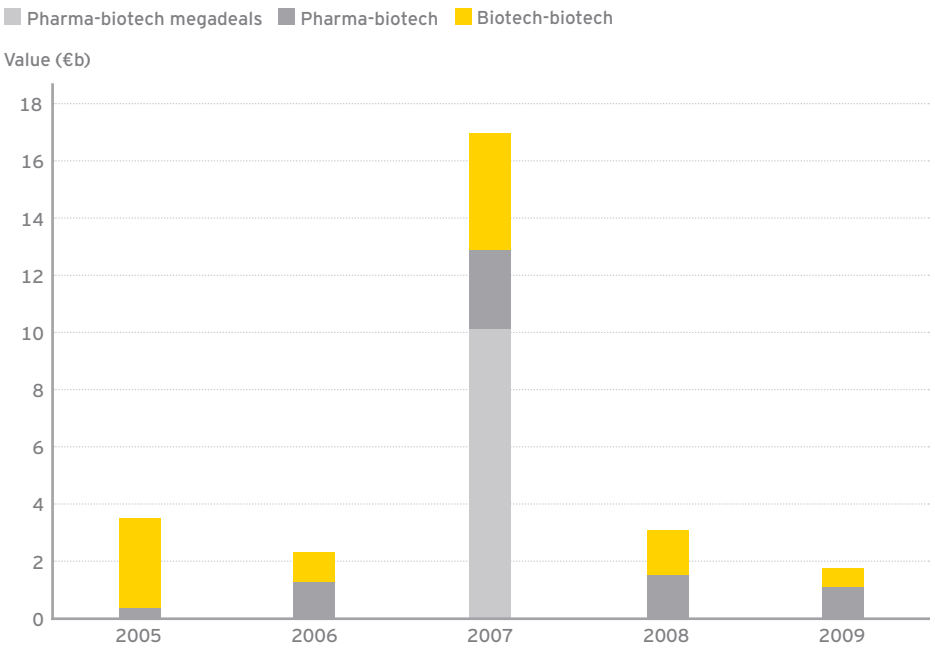
After a strong showing in 2007, M&A activity in Europe has declined significantly. In 2008, the total value of M&As involving a European biotech company declined to only €3.1 billion (US$4.3 billion), and then fell even further in 2009, to €1.8 billion (US$2.5 billion).

There were few significant M&A transactions involving European biotechs in 2009. The most significant transaction not involving CVRs was the merger between Biovitrum and Swedish Orphan International, valued at €337 million (US$470 million). The combined company has a significant portfolio of niche drugs on the market and in development. There were three other transactions with potential values of at least €300 million (US$418 million), but all three included CVRs. These were the previously mentioned Alcon acquisition of ESBATech, sanofi-aventis' takeover of France-based ophthalmic company Fovea Pharmaceuticals for up to €370 million (US$516 million; milestones were not disclosed) and AstraZeneca's acquisition of Novexel for US$505 million (including milestones of US$75 million).

Alliances

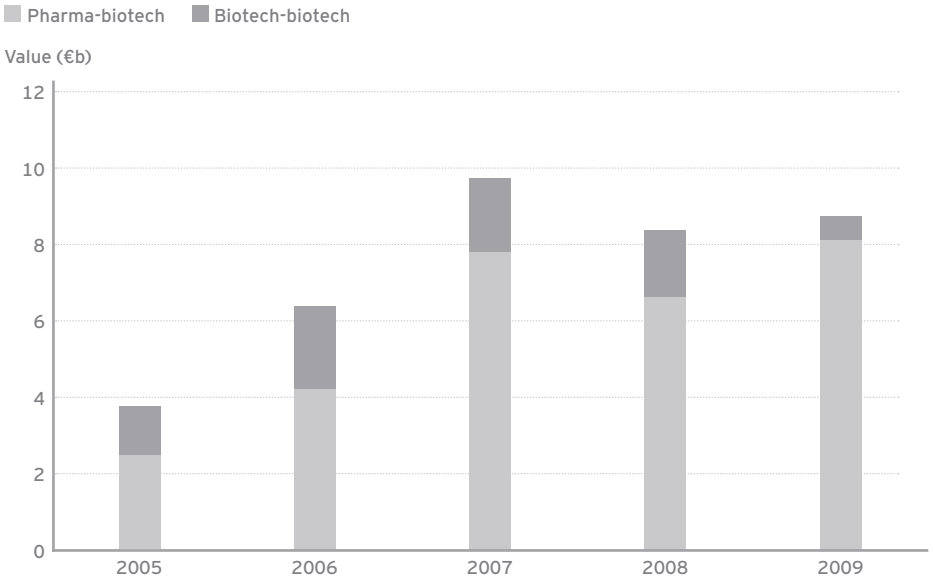
In both 2009 and 2008, there were 57 alliances with financial terms disclosed involving European biotech companies. The

European M&As, 2005–09



Source: Ernst & Young, Windhover Information, MedTRACK, BioWorld and company news via NewsAnalyzer

European alliances held steady in 2009



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

total potential value of these transactions was also relatively unchanged, at €8.7 billion (US$12.1 billion) in 2009 compared to €8.4 billion (US$11.7 billion) in 2008. The 2009 total includes the two significant equity investments made by Johnson & Johnson, in Crucell and Elan (discussed earlier). Excluding these transactions, there were 35 deals with disclosed up-front payments, which aggregated €710 million (US$990 million), while 2008 saw 40 transactions with an aggregate value of €610 million (US$851 million). The average up-front payment disclosed increased to €20 million (US$27.9 million) from €16 million (US$22.3 million) in 2008, while the median up-front decreased to €7 million (US$9.8 million) from €8 million (US$11.2 million). We count 10 transactions with up-front payments of €20 million (US$27.9 million) or greater (again excluding the J&J investments noted above), which comprised 74% of total up-front payments in 2009. In 2008, there were 8 such transactions which comprised 68% of total upfont payments.

Canada

While financing for Canadian public companies fell to a 10-year low, there was a significant increase in partnering activities in 2009 — a positive development for the Canadian industry. For the first time, there were six licensing agreements signed by Canadian biotech companies with potential values in excess of US$100 million each. The largest licensing agreement was Cardiome Pharma's deal with Merck, whereby Merck acquired exclusive global rights to an oral formulation of vernakalant to treat atrial fibrillation. This involved more than US$60 million in up-front payments and US$640 million in potential regulatory and commercial milestones and royalties. The second-largest deal was the deal between OncoGenex and Israel's Teva Pharmaceuticals for OGX-011, a Phase III cancer therapy. This transaction involved a US$60 million initial cash payment, which was a combination of equity, prepayment of development costs and up-front fees. This agreement could result in additional payments of more than US$370 million for royalties and milestones. The remainder of the deals were also interesting, as up-front payments in all cases exceeded US$10 million. Canadian companies did not just out-license assets, however. Biovail entered into a collaboration and license agreement with US-based ACADIA Pharmaceuticals where the company in-licensed US and Canadian rights to develop and commercialize primavaserin, a Phase III drug with a US$30 million up-front payment and US$160 million in development milestones, as well as significant royalties. This agreement also provides for significant further payments for other indications.

On the M&A front, Montreal-based Nventa Biopharmaceuticals was acquired by US-based Akela Pharma in a stock deal worth C$1.4 million (US$1.2 million).

Australia

With the IPO window closed for Australian companies, there was some activity in M&As. Early in 2009, Arana was acquired by US-based Cephalon for A$319 million (US$223 million). There was much speculation that this sizeable acquisition would lead to a wave of consolidation in Australia. As it turned out, a number of small deals followed, but there was only one other significant acquisition during the year — the purchase of Peplin by Denmark-based Leo Pharma for A$318 million (US$207 million).

On the strategic alliance front, the first quarter of 2010 saw Acrux enter into an exclusive worldwide license agreement with Eli Lilly for its AXIRON male testosterone product for which its new drug application is currently undergoing review by the FDA. This significant deal includes an up-front payment of US$50 million and other milestone payments and benefits in excess of US$280 million.

Other markets

For noteworthy deals in other markets, refer to the *Country profiles* section.

Outlook

While there was some slowdown in transaction activity during 2009 — particularly for M&As — the challenges motivating these transactions have not eased. The new normal is therefore likely to feature an active deal environment. We expect to see continuing consolidation of commercial-stage (or nearly commercial-stage) companies with market capitalizations under US$10 billion. At the end of 2009, there were 26 companies in the US and eight firms in Europe with a market capitalization of between US$1 billion and US$10 billion. Of these, 26 were generating revenue from marketed products and 7 of the remainder had products in Phase III or awaiting approval.

In addition to strong alliance activity, and the continued use of options, we can also expect to see increased use of creative deal structures as both investors and companies look to deploy capital efficiently and share drug development risk. In this regard, we expect to see companies formed to in-license pipeline candidates from big pharma and big biotech companies, with the licensor retaining an option to reacquire the products at a later date for a premium — similar to the Symphony Capital structure that has been so visible in recent years. ▶

Dan Zabrowski
Roche
Global Head, Roche Partnering

Striking a healthy balance

While the last year has been difficult for those seeking short-term gains from biotech investments, ours has always been an inherently risky business. But history has also shown that a long-term perspective focused on patients' needs and genuine innovation is a proven path to success.

At Roche, accessing external innovation has long been critical to our business, and this is set to continue. Last year, we consolidated our leading position in biotechnology by "privatizing" Genentech. This decision was not driven by volatile markets or speculation about the impact of health care reforms. Rather, it was the result of a successful 20-year relationship that nurtured scientific innovation. This move — which aims to enhance our combined innovation while maximizing operational efficiencies — makes sense at a time when payors are putting downward pressure on prices and regulatory demands are driving up the cost of drug development. In addition, it has boosted Roche's strength and scale in the US, while the Genentech Research and Early Development organization has remained an independent innovation center in the Roche Group.

When Roche's alliance with Genentech was first struck in 1990, few could have predicted how significant biotechnology would become in treating life-threatening diseases, but an early investment with a long-term view has certainly paid dividends. Today, biologics account for around two-thirds of our pipeline and almost half our revenues.

Scientific innovation may provide the opportunities, but technologies by themselves do not ensure success. Regardless of their size or stage of development, companies need an overriding strategy for developing medicines from technologies. Novel drugs that can prove meaningful clinical differentiation will continue to be reimbursed, accelerating the drive toward personalized health care solutions that fit treatments to patients.

One of Roche's most exciting compounds, RG7204, is currently in Phase III and demonstrating very promising results in melanoma patients who previously had few options. Concurrently, our colleagues in Roche Diagnostics are developing a companion diagnostic for the drug to ensure the right patients receive treatment targeted for their condition. The high level of excitement generated in the medical and patient communities after we presented Phase I results demonstrates society's hunger for true breakthroughs in medicine.

We have long believed that we don't have a monopoly on innovation. Indeed, RG7204 was developed in partnership with California-based Plexxikon, and half our late-stage new molecular entities (NMEs) over the last three years have been partnered compounds. Striking that healthy balance between internal and external innovation is now more important than ever as big pharma faces the patent cliff. Some firms are taking drastic measures to shift the balance from internal to external research, while others are diversifying into less risky businesses. Roche will continue to focus on medically differentiated therapies, concentrating entirely on prescription pharmaceuticals and in vitro diagnostics.

We intend to expand our relationships with the biotech community. Year-on-year, we continue to do more deals; our total last year was up by 50% since 2007. We work closely with our scientists to pick potential winners. Since programs are reviewed and assessed using the same criteria regardless of origin, our researchers drive partnered projects forward with the same passion and energy as our homegrown programs. The results are evident. Of the 19 clinical-stage deals signed by Roche or Genentech since 2004, 60% remain active in the R&D portfolio.

The biotech industry has every reason for optimism. Scientific advances show no sign of slowing, and pharma is willing to invest in high-quality assets and technologies. Most important, there remains a huge need to treat uncured diseases. At Roche, that necessity will continue to be our driving force in looking for new partnerships. We look for first-in-class or best-in-class compounds and technologies that have the potential to change the standard of care. A strong preclinical package and biomarker strategy are important, as is a proven ability to deliver. Our strategic therapy areas are oncology, CNS, metabolism, virology and inflammation. In return, we offer tailored deal structures that accommodate the needs and growth ambitions of partners, together with a seat at the development table to ensure that decision-making takes into account the best available expertise from internal and external sources.

Ultimately, maintaining a healthy balance between internal and external innovation will boost the industry's growth while providing returns for investors and, most importantly, benefits for patients. ►

Products and pipeline

Steady growth

In many ways, 2009 looked much like 2008 in terms of product and pipeline developments. The US Food and Drug Administration (FDA) approved 29 new molecular entities (NMEs) and biologic license applications (BLAs) — about the same number as in 2008, when 27 were approved. Approvals by the European Medicines Agency (EMA) also remained relatively flat. The number of drug candidates in the clinical pipelines of European companies increased by 16% during the year — also on par with the growth seen in recent years. Phase II programs led the growth, with a 22% increase over 2008.

United States

Approvals: steady progress

After years of insufficient staffing levels, the FDA launched a hiring initiative in 2008 to increase headcount by 1,300 new employees. The FDA was increasing staffing levels not only to improve the percentage of reviews in which it meets priority and standard review deadlines — which according to a study in *Nature* were 69% and 83% in 2009, respectively — but also to meet its responsibility to regulate tobacco starting in June 2009. However, 2009 was also a year with a massive pandemic scare that required regulatory agencies to respond rapidly with fast-track approval for an H1N1 vaccine. Also, a lag time exists between the time a new employee joins the FDA and comes fully up to speed in a way that could impact the overall performance goal of meeting 90% of the priority and standard review times. Considering those factors, there is reason to hope that the hiring increase could translate into faster approval times in years ahead.

After reaching an all-time low in 2007, FDA drug approval numbers have rebounded slightly in 2008 and 2009. In 2009, the FDA approved 29 new products, including 25 NMEs and BLAs approved by the Center for Drug Evaluation and Research (CDER) and four BLAs approved by the Center for Biologics Evaluation and Research (CBER). (These totals do not include vaccines approved by CDER or CBER.) Products granted approval in 2009 were in therapeutic categories that have traditionally led product approvals, including five approvals in cancer and four approvals for neurological disorders.

A number of the products approved were developed by US biotechnology companies. For instance, in the case of Fanapt, approved in May 2009 for the treatment of schizophrenia, Novartis acquired the US and Canadian commercialization rights from Vanda Pharmaceuticals in October. The drug had previously changed hands numerous times. (For more details, refer to the *Deals* article.) In June, AMAG gained marketing approval for Feraheme, its treatment of iron deficiency anemia (IDA) in adult patients with chronic kidney disease. Before approving it in 2009, the FDA had twice delayed Feraheme (in October 2008, through a complete response letter requesting additional clinical information and the addressing of certain manufacturing deficiencies, and again in December 2008).

The second half of the year was very productive for biotech company approvals. In September, Ista Pharmaceuticals' ophthalmic solution, Bepreve, was approved for ocular itching associated with allergic conjunctivitis. That same month, Allos Therapeutics gained approval for its relapsed peripheral T-cell lymphoma therapy, Folotyn, while Theravance gained approval for its treatment of complicated skin and skin structure infections (cSSSIs), Vibativ. In November, Dyax Corporation received FDA approval for its drug Kalbitor — a competing product to Lev Pharmaceuticals' 2008 approved product, Cinryze — for sudden attacks of hereditary angioedema (HAE).

Success: pipeline surprises

Two biotech companies, Dendreon and Human Genome Sciences, received positive, late-stage clinical results for their drug candidates that resulted in sharp upticks in their stock performance in 2009. (See this year's financing article, "A higher bar," for more information).

The FDA had initially rejected Dendreon's Provenge in 2007 because of insufficient clinical data. This experimental prostate cancer therapy is designed to activate a patient's own immune system by taking cells from a patient's tumor, incorporating them into a vaccine and injecting the cells back into the patient to elicit an immune response. The rejection was issued despite an overwhelming recommendation from an outside advisory panel for the drug's approval. With patients left with limited choices for advanced prostate cancer that has spread outside the prostate gland, Dendreon continued work on Provenge and completed an additional Phase III study. In April 2009, Dendreon announced the results of the study, which demonstrated median survival rates had been extended by about four months. The positive news gave the company a major boost with investors, as its market value skyrocketed from US$440 million (US$4.62/share) at

the beginning of the year to nearly US$3.5 billion (US$26.40/share) by year-end. Dendreon expects a complete response letter from the FDA in 2010.

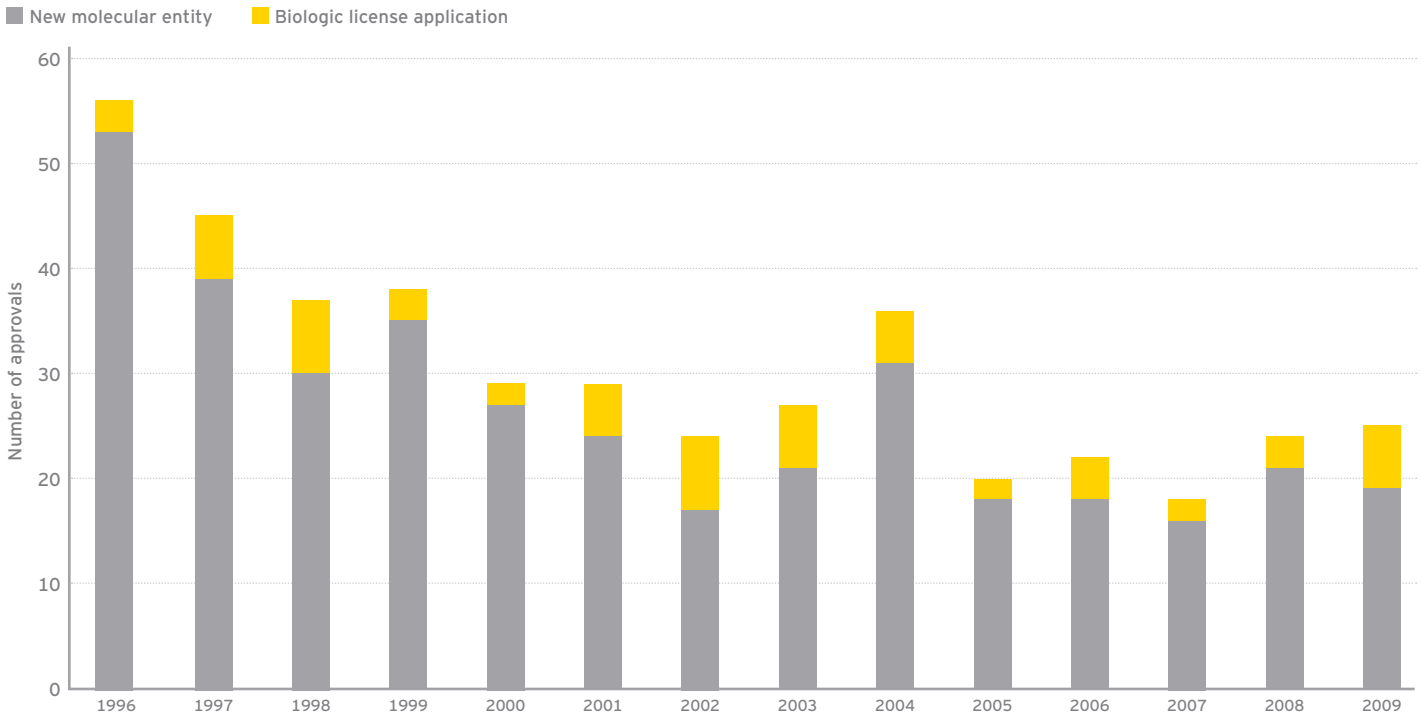
Human Genome Sciences (HGS) received a similar boost from positive pipeline news. HGS and GSK announced in 2009 that BENLYSTA (belimumab, formerly LymphoStat-B) met the primary endpoint in the first of two pivotal Phase III trials in patients with serologically active systemic lupus erythematosus (SLE). On the day of the announcement, the company's share price jumped from US$3.32 to US$12.51. HGS ended the year with a market value more than 19 times greater than its value on 1 January.

Selected approvals by US companies, 2009

Company	Brand name	Generic name	Type of approval	Indication	REMS required	Month	Orphan designation	Approved/ registered in
Allos Therapeutics	Folotyn	pralatrexate	New molecular entity	Relapsed or refractory peripheral T-cell lymphoma		Sept. 2009	Yes	US
AMAG	Feraheme	ferumoxytol	Biologic license application	Iron deficiency anemia (IDA)		June 2009		US
Gloucester	Istodax	romidepsin	New molecular entity	Cutaneous T-cell lymphoma		Nov. 2009	Yes	US
Dyax	Kalbitor	ecallantide	Biologic license application	Hereditary angioedema (HAE)	Yes	Nov. 2009	Yes	US
Gilead Sciences	Cayston	aztreonam	New chemical entity	*Pseudomonas aeruginosa* lung infections		Sept. 2009	Yes	EU (US approved in Feb. 2010)
IDM	Mepact	mifamurtide	New chemical entity	Resectable non-metastatic osteosarcoma		Mar. 2009	Yes	EU (also approved in other markets)
Ista Pharma	Bepreve	bepotastine besilate	New molecular entity	Ocular itching associated with allergic conjunctivitis		Sept. 2009		US
GTC Biotherapeutics (licensed by Lundbeck)	ATryn	recombinant antithrombin	Biologic license application	Antithrombin deficiency		Feb. 2009	Yes	US (previously approved in EU)
Vanda Pharma (licensed by Novartis)	Fanapt	iloperidone	New molecular entity	Schizophrenia		May 2009		US
Ovation	Sabril	vigabatrin	New molecular entity	Complex partial seizures	Yes	Aug. 2009	Yes	US (previously approved in other markets)
Regeneron	Arcalyst	rilonacept	New molecular entity	Cryopyrin-Associated Periodic Syndromes (CAPS)		Sept. 2009	Yes	EU (previously approved in US)
Theravance	Vibativ	telavancin	New molecular entity	Complicated skin and skin structure infections (cSSSIs)	Yes	Sept. 2009		US

Source: Ernst & Young, EMA, FDA and company websites

FDA product approvals, 1996–2009



Source: Ernst & Young, FDA
Chart shows product approvals by the FDA's Center for Drug Evaluation and Research.

Europe

Pipeline strength: continued growth

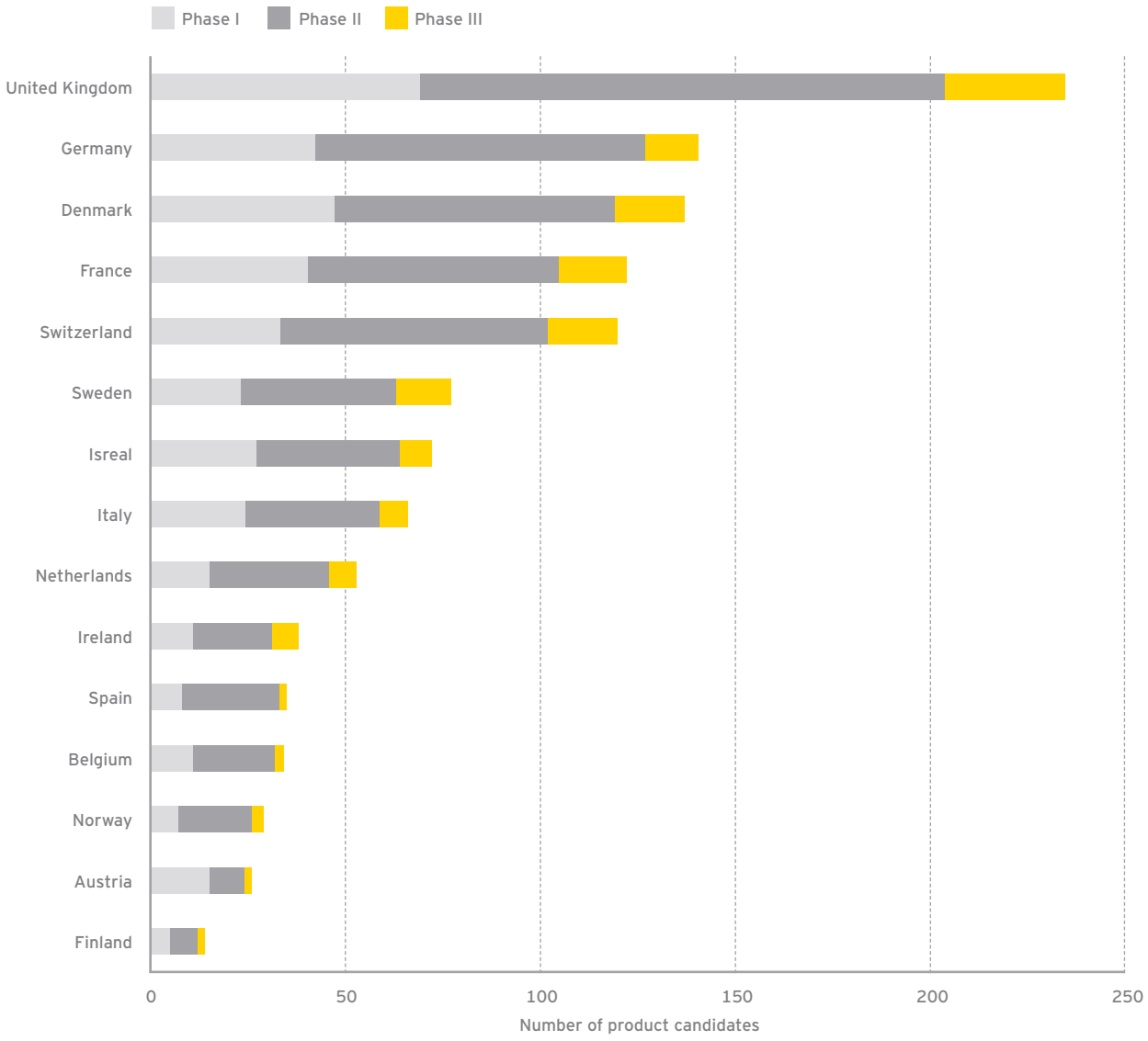
The total number of drugs in clinical development in Europe climbed to 1,199 in 2009, a 16% annual increase that is relatively on par with the growth seen over the last several years. Phase II programs led the growth with an increase of 120 products (22%) over 2008. There were also increases in late- and early-stage development, with a 12% increase in Phase III and 7% increase in Phase I products.

UK-based companies continue to lead the European pipeline, accounting for 20% of products in clinical development, on par with their share in 2008. The majority of clinical programs in development (71%) for British companies are in Phase II or later. Germany and Denmark were in second and third place in 2009, with their companies accounting for 12% and 11% of the European clinical pipeline. France and Switzerland round out the top five countries, with each representing about 10% of developmental programs. The relative positions of the top five are unchanged from 2008.

Swiss companies' contribution to the overall European pipeline had declined in the past couple of years because of the acquisitions of prominent Swiss biotech players, including Speedel (acquired by Novartis in 2008) and Serono (acquired by Merck KGaA in 2007). In 2009 – in the absence of any such large Swiss acquisitions – the aggregate pipelines of Swiss companies increased by a healthy 20%. Israeli companies also had a big year in stoking their clinical pipelines, as they increased their clinical development portfolio by 26% and overtook Italy to reach the number seven spot.

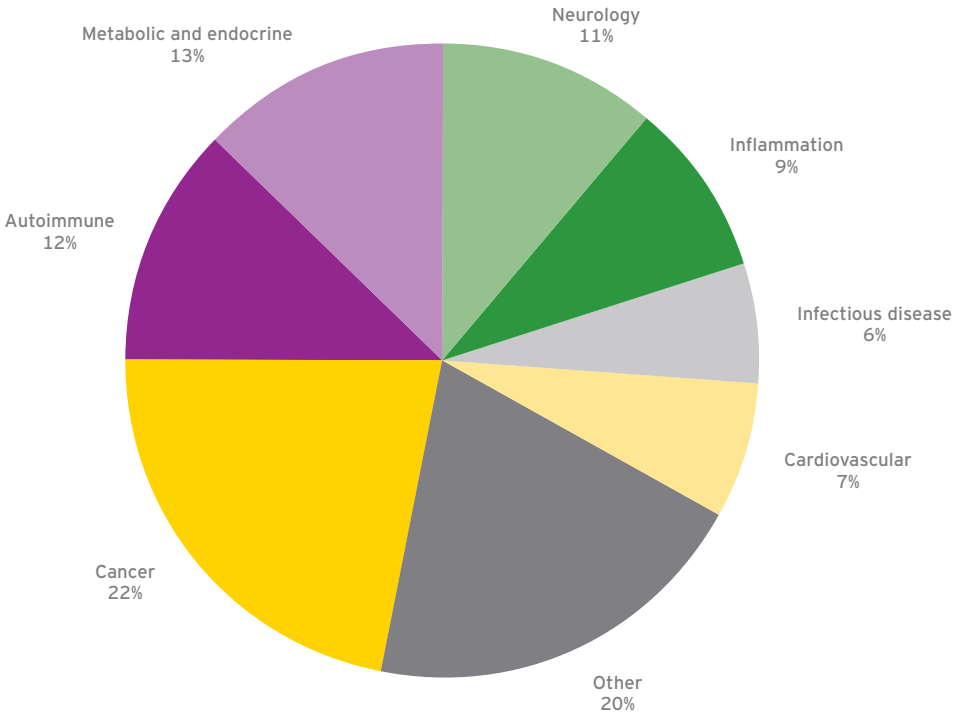
As in previous years, cancer therapeutics led the European drug pipeline with 22% of Phase III candidates in development. The oncology segment has declined somewhat from levels seen in 2007, when oncology made up 28% of the late-stage pipeline. The "metabolic and endocrine" and "autoimmune" indications rounded out the top three late-stage development therapeutic categories, representing 13% and 12%, respectively.

European clinical pipeline by country, 2009



Source: Ernst & Young, MedTRACK and company websites

European Phase III pipeline by indication, 2009



Source: Ernst & Young, MedTRACK and company websites

European approvals

The EMA was active in approving products for a variety of therapeutic categories, including cancer, neurology, cardiovascular, metabolic disorders and immunology. Most products approved by the EMA were from US-based companies or large pharmaceutical organizations; however, a handful of European-based biotechs secured approvals as well.

Belgium-based TiGenix received EMA approval for ChondroCelect, a cartilage-repair therapeutic, in October. The cell-based medicinal product consists of chondrocytes (cartilage-forming cells) that are taken from a healthy region of a patient's cartilage, grown outside the body, and then surgically re-implanted. Belgium-based UCB also garnered market approval in Europe for its drug Cimzia for rheumatoid arthritis. Cimzia had previously gained US marketing authorization for moderate-to-severe Crohn's disease.

Other approvals included Ferring Pharmaceutical's Firmagon in February for patients with advanced prostate cancer. Firmagon was previously approved by the FDA in 2008. Orphan Europe's product Vedrop was approved for cholestatis, a condition in which the flow of bile from the liver is blocked. Victoza, a Novo Nordisk product, was approved for type 2 diabetes in June.

European companies also received FDA approval for a number of products in 2009. GlaxoSmithKline received accelerated approval in October 2009 for Arzerra, a treatment for refractory chronic lymphocytic leukemia. Arzerra, which GSK obtained through a collaboration with Genmab, is a monoclonal antibody that causes the body's immune response to fight against normal and cancerous B-cells. Azerra went on to receive conditional approval in Europe in January 2010 for the treatment of refractory chronic lymphocytic leukemia (CLL), but only for the approximately 25% or so of patients who do not respond to the standard therapies fludarabine and alemtuzumab, which EMA has already approved.

Lundbeck secured two approvals in 2009. Its Sabril, for treatment of infantile spasms in pediatric patients and refractory complex partial seizures in adults, was approved in August 2009. Earlier in the year, Lundbeck licensed Atryn from GTC Biotherapeutics and received approval for the antithrombin deficiency medication in February.

In another licensing deal, Cypress Bioscience licensed Savella from French drug-maker Pierre Fabre and then signed a commercialization agreement with Forest Laboratories. In January, the FDA approved the product for the treatment of fibromyalgia. Milnacipran was originally approved in France in 1996 for major depression episodes but was introduced in the United States for the first time with the fibromyalgia indication.

Outcomes-based pricing arrangements

Facing mounting pricing pressures, payors are seeking ways to leverage pay-for-performance reimbursement mechanisms. In this environment, risk-sharing pricing arrangements – where

Selected product approvals by European companies, 2009

Company	Brand name	Generic name	Type	Month	Indication	Orphan designation	Approved/ registered in
Ferring Pharmaceuticals	Firmagon	degarelix	New chemical entity	Feb. 2009	Prostate cancer		EU (previously approved in the US)
Genmab/ GlaxoSmithKline	Arzerra	ofatumumab	Biologic license Application	Oct. 2009 (US) Jan. 2010 (EU)	Chronic lymphocytic leukemia (CLL)	Yes	US (EU approved in Jan. 2010)
Ipsen (licensed to Medicis)	Dysport		Biologic license Application	Apr. 2009	Cervical dystonia/ frown lines	Yes	US
Novo Nordisk	Victoza	recombinant liraglutide	New chemical entity	June 2009	Type 2 diabetes		EU (US approved in Jan. 2010)
Octapharma	Wilate	vWF/Factor VIII Complex	Biologic license Application	Dec. 2009	von Willebrand's disease (VWD)	Yes	US
Orphan Europe	Vedrop	tocofersolan	New chemical entity	Jul. 2009	Vitamin E deficiency		EU
Pierre Fabre (licensed to Cypress Bioscience/Forest Laboratories)	Savella	milnacipran	New molecular entity	Jan. 2009	Fibromyalgia		US
Recordati (licensed from Kissei Pharmaceutical)	Silodyx/Urorec	silodosin	New chemical entity	Feb. 2010	Benign prostatic hyperplasia (BPH)		EU (previously approved in the US, Japan)

Source: Ernst & Young, EMA, FDA and company websites

drug companies incur some portion of the cost of treating patients that do not respond to an intervention — are becoming increasingly common as payors seek to pay based on health outcomes.

This approach has been most visible in the UK, where the National Institute for Health and Clinical Excellence (NICE) makes coverage decisions for the National Health System (NHS). After first appearing a couple of years ago, the number of such arrangements mushroomed in 2009 — a sign of the times and a potential harbinger of things to come in other global regions.

As shown in the accompanying table, the lion's share of such arrangements continues to be in the UK. Recent examples include Celgene's arrangement for obtaining coverage for Revlimid, its multiple myeloma drug. NICE initially rejected Revlimid in 2008 on the grounds that the therapy was not cost effective, but Celgene secured approval in April 2009 with an outcomes-based pricing arrangement under which NHS pays for the first two years of treatment in patients who have received at least one prior therapy. If treatment is required after two years, Celgene will cover the costs (excluding related costs such as hospitalization), thereby reducing the financial burden on the NHS.

There are signs the trend is starting to spread to other markets. In the US, for instance, Merck signed an agreement with insurance giant CIGNA that provides CIGNA customers increased discounts on Merck's

Anthony Masherelli
Ernst & Young LLP

A closer look

Uncertain by design: preparing for outcomes-based pricing arrangements

As pricing pressures have intensified in recent years, outcomes-based pricing arrangements have become increasingly visible in some markets. These agreements represent a paradigm shift for the industry, since they reimburse drug companies based not on how many units of a product they sell, but rather on how effective those products are in delivering health-related outcomes. With health care reform initiatives in many countries intensifying the focus on health care costs, such arrangements could become even more common. Beyond the strategic implications, these arrangements also present operational challenges for drug companies.

Data matters

A recent report by Datamonitor classifies outcomes-based pricing arrangements into three broad categories: **clinical risk-sharing**, where a payor receives a refund from the manufacturer if the drug fails to meet clinical outcomes; **cost-effectiveness risk-sharing**, where a payor receives a refund if cost-effectiveness targets are not met; and **fixed budget, price or volume agreements**, where the amount a payor pays is limited by provisions such as price caps, utilization caps and budget caps.

Clinical risk-sharing arrangements, in particular, carry significant data-collection challenges. To track and evaluate outcomes, companies must maintain large volumes of relevant patient-level data, without which they may be exposed to significant reimbursement risk. The data collected needs to permit reliably measuring clinical results — which may not be easily accomplished for every therapy.

To address these challenges, companies should consider several factors:

- **Pick the right measure.** Performance measures should be selected carefully based on clinical-trial results and post-marketing studies. Measures should lend themselves to objective evaluation, since guarantees based on subjective measures or long evaluation periods could lead to commercial disputes with payors over outcomes, require maintaining significant outcomes data for extended periods and raise the potential for long-term revenue deferral.
- **Monitor patients.** Companies should consider effective patient monitoring and assistance programs to facilitate patient compliance, which can increase the likelihood of favorable outcomes.
- **Boost information technology and management.** Companies will need to ensure that their information technology (IT) systems are up to these challenges. Existing systems may need to be upgraded to track the right metrics. Information management is also important. Financial reporting personnel will likely need greater access to clinical outcomes data to account for outcomes-based arrangements, and companies will need to facilitate data access while protecting patient privacy. And since this data may become a critical input into the financial reporting process, firms will need controls to ensure information is complete and accurate.

Accounting implications

It's not surprising that outcomes-based pricing arrangements raise significant revenue recognition challenges. How much revenue can a company recognize — and *when* can it recognize it — in an arrangement where there is tremendous uncertainty about how much it will ultimately be paid?

As is often the case, the answer will ultimately depend on the specific facts and circumstances of each arrangement. In some cases, companies will need to defer revenue until patient outcomes are known or can be reliably estimated. In others, they may be able to recognize full or partial revenues at the time of sale.

In some arrangements (particularly those involving clinical risk sharing) the timing of revenue recognition will depend on a company's ability to estimate, at the time of sale, the revenue it will ultimately receive in connection with a sale — in other words, whether the arrangement fee is fixed or determinable (US GAAP) or can be measured reliably (IFRS) at the time of sale. Depending on the nature of the arrangement, this determination may prove challenging.

Given current industry trends, it seems inevitable that we will see more outcomes-based pricing arrangements over time. It is also inevitable that these structures bring more uncertainty for companies. To manage this risk, firms should consider accounting implications up front and should align program design to the availability of clinically relevant information and IT capabilities.

Selected outcomes-based pricing agreements

Drug	Indication	Company	Date	Agreement with	Market	Description
Aclasta (zoledronic acid)	Osteoporosis	Novartis	May 2009	Multiple sick funds, Agenzia Italiana del Farmaco (AIFA)	Germany, Italy	Novartis will reimburse health authorities for Aclasta if bone fractures occur for compliant patients.
Actonel (risedronate sodium)	Osteoporosis	P&G and sanofi-aventis	Apr. 2009	Health Alliance	US	The companies cover average expenses to treat certain fractures in women correctly taking Actonel by proportionally reducing Health Alliance's cost of purchasing Actonel.
Januvia (sitagliptin)/ Janumet (metformin and sitagliptin)	Type 2 diabetes	Merck	Apr. 2009	CIGNA Corporation	US	Merck gives discounts to CIGNA if patients take drugs as prescribed and further discounts/rebates if patients lower blood sugar levels even by methods other than taking Merck's diabetes drugs.
Lucentis (ranibizumab)	Wet age-related macular degeneration	Novartis	Aug. 2008	NICE/NHS	UK	NHS pays for first 14 treatments; Novartis pays for any subsequent injections.
Nexavar (sorafenib)	Advanced renal cell carcinoma	Bayer	Nov. 2006	Servizio Sanitario Italiano (SSN)	Italy	Bayer gives SSN 50% discount for first three months of treatment, after which SSN is fully reimbursed for non-responders.
Nexavar (sorafenib)	Liver cancer	Bayer	Nov. 2006	SSN	Italy	SSN pays full price for first two months of treatment, after which SSN is fully reimbursed (and treatment is stopped) for non-responders.
Revlimid (lenalidomide)	Multiple myeloma	Celgene	Apr. 2009	NICE/NHS	UK	NHS pays for treatment for the first two years in patients who have received at least one other therapy. Celgene will pay if treatment is required after two years.
RoActemra (tocilizumab)	Rheumatoid arthritis	Roche	Mar. 2010	Agency for Health Technology Assessment	Poland	Price will be reduced to that of "initiating therapy" (Amgen's Enbrel) for two years; subsequent coverage based on safety data.
Sutent (sunitinib)	Renal cell carcinoma	Pfizer	Mar. 2009	NICE/NHS	UK	5% price cut and six weeks of free treatment; subsequently, NHS will only pay for responding patients.
Tarceva (erlotinib)	Non-small-cell lung cancer	Roche	Nov. 2008	NICE/NHS	UK	NHS pays only on condition that overall treatment costs (including administration, adverse events and monitoring) are equal to that of sanofi-aventis' Taxotere.
Tyverb (lapatinib)	Breast cancer	GlaxoSmithKline	June 2009	AIFA	Italy	AIFA monitors patients for 12 weeks and reimburses costs for patients for whom disease progression has been halted; otherwise GSK pays.
Velcade (bortezomib)	Multiple myeloma	Janssen-Cilag	July 2007	NICE/NHS	UK	NHS pays for responding patients; J&J reimburses cost for non-responders.
Yondelis (trabectedin)	Advanced soft tissue carcinoma	PharmaMar	Dec. 2009	NICE/NHS	UK	NHS pays for first five treatment cycles; PharmaMar pays for any subsequent cycles.

Source: Ernst & Young, Datamonitor, media reports

oral anti-diabetes medications Januvia and Janumet if patients take the drugs as prescribed. Additionally, CIGNA will receive further discounts/rebates if patients lower blood sugar levels, even by methods other than taking Merck's diabetes medications.

These pricing models – where firms get paid based on outcomes rather than sales volume – are uncharted territory for most companies, and present new sources of risk. As these arrangements become more prevalent, companies will need to focus on ways to address challenges such as effectively managing data and appropriately accounting for these transactions. (For more information, see *A closer look* on page 92.)

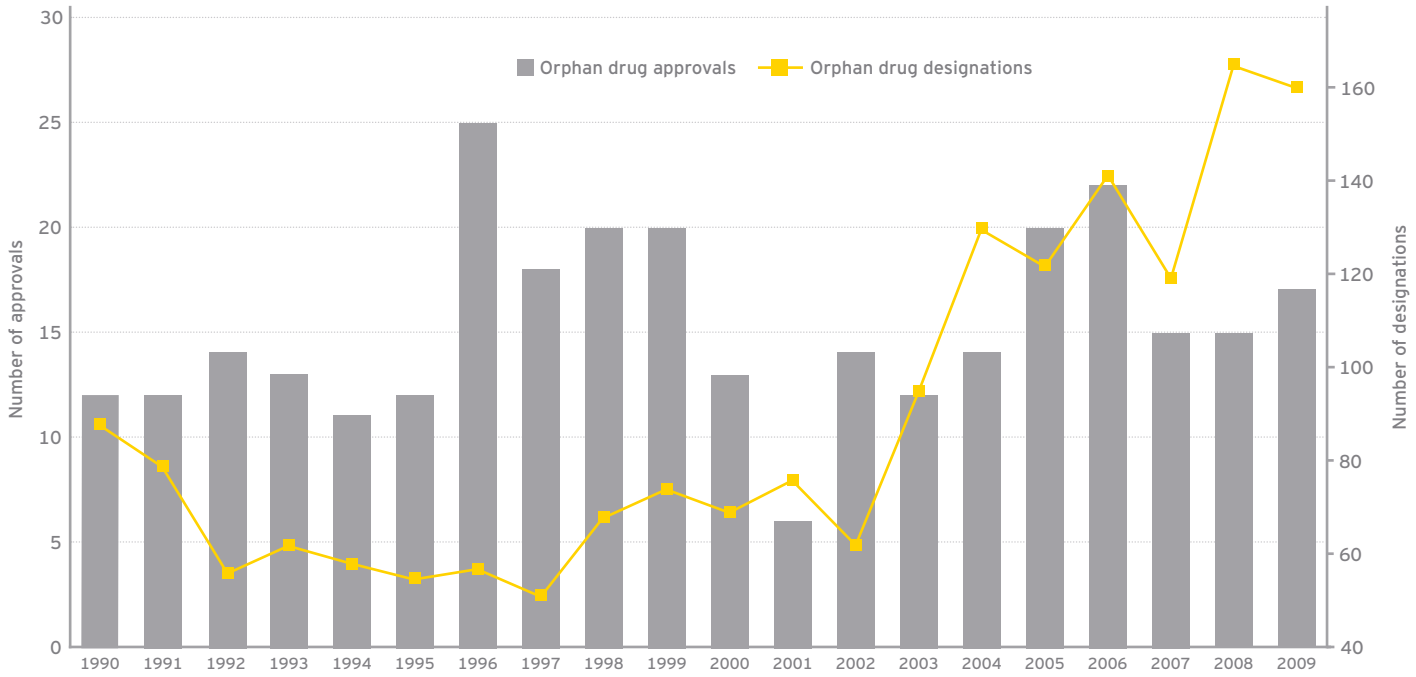
Orphan drugs

The FDA approved 17 orphan drugs in 2009, including 11 NMEs or BLAs and six products with expanded indications – the largest total since 2006, when 22 drug indications received approval. The agency also gave more than 160 indications orphan drug designation; slightly lower than the 165 in 2008 but markedly higher than the levels seen earlier this decade.

Orphan drug approvals have been on an upward trajectory over the last decade. According to a Tufts University study, approvals of orphan drug designations in the US more than doubled from 208 in 2000–02 to 425 in 2006–08.

Biotech firms have traditionally been significant players in this segment. To some extent, this was because the economics of

FDA orphan drug approvals and designations, 1990–2009



Source: Ernst & Young, FDA

orphan drugs were challenging for larger organizations, which were focused on high-volume blockbusters. Now, with the end of the blockbuster era, the economics are changing and moving the focus to small patient populations and therapeutics that focus on severe, unmet medical conditions where a differentiated patient outcome can be demonstrated. As a result, orphan drugs are getting some serious consideration from big pharma. For instance, Gaucher's Disease, a genetic condition in which a fatty substance accumulates in cells and certain organs, currently affects 1 in 50,000–100,000 people. Pfizer entered an agreement with Israel-based Protalix in December 2009 for the development and commercialization of its product taliglucerase alfa. Taliglucerase alfa is the first enzyme replacement therapy derived from a proprietary plant cell-based expression platform using genetically engineered carrot cells.

Also for Gaucher's, in September 2009, the FDA gave Shire's product VPRIV a fast-track approval designation. Prior to its eventual approval in February 2010, VPRIV was being prescribed to Gaucher's patients on an emergency basis for several months due to the shortage of Genzyme's Cerezyme, a result of manufacturing problems in the middle of 2009.

Adapting to REMS

In response to growing concerns about product safety, The Food and Drug Administration Amendments Act of 2007 created the Risk Evaluation Mitigation Strategy (REMS) program to manage drug safety risks after products have been brought to market. The FDA can require REMS from manufacturers when it finds they are necessary to ensure that products' benefits outweigh their risks. A REMS typically includes a medication guide as well as a communication plan to discuss side effects and potential adverse effects of the approved product with physicians.

In 2009, the FDA continued to rely on the REMS program as a core component of its approach to approving products. As of March 2010, the FDA has approved a total of 107 REMS, up from 21 that had been approved as of December 2008. Eleven of the 29 (38%) NME and BLA drug approvals had REMS in 2009, which is relatively consistent with 2008, when one-third of products were approved with REMS. In the long run, many hope REMS can help reduce approval times and get new drugs to patients faster.

Drug manufacturers have had to adapt by preparing for the possibility of a REMS requirement prior to applying for an NDA, since a launch could get postponed if a company is not prepared to comply. As the program proceeds, most companies will acquire experience producing a REMS, and it will naturally become a part of the application process checklist.

In some instances, the REMS program has provided a "second life" for drug approvals, as was the case with sanofi-aventis' Multaq, a drug for abnormal heart rhythm called atrial fibrillation (AFib). The FDA had originally rejected Multaq in 2006 after linking the therapy to a higher death rate. In 2009, however, sanofi-aventis gained market approval with a REMS after a study showed a significant reduction in the rate of hospitalizations due to AFib. In conjunction with the launch of Multaq, the company launched a program to assist health care professionals in identifying appropriate patients to ensure safe use of the product while mitigating risks.

The REMS regulations also can be applied to therapies that are already on the market. For example, Centocor, Ortho Biotech (both subsidiaries of Johnson & Johnson) and Amgen received approval for REMS in February 2010 for their erythropoiesis-stimulating agents (ESAs), which include Procrit, Aranesp and Epogen. The FDA required Amgen to develop a program because studies showed an increase in risk of tumor growth, heart attack, heart failure, stroke or blood clots in patients using ESAs. The program provides patients with a medication guide explaining the risks and benefits associated with using ESAs.

Outlook

At the beginning of a new decade, biotech company pipelines show strength, but there are still challenges and risks ahead. While product approvals held steady in 2009, it will be challenging for many companies to continue to fund R&D at historic levels given today's tight capital market environment. With the increase in FDA budget and payrolls, as well as the appropriate application of a REMS, drug manufacturers are hoping for some relief from regulators in the form of shorter approval times in the years ahead. ▶

Edward Abrahams
Personalized Medicine Coalition
President

Perspectives on personalized medicine

What one thing would you change to accelerate the adoption of personalized medicine?

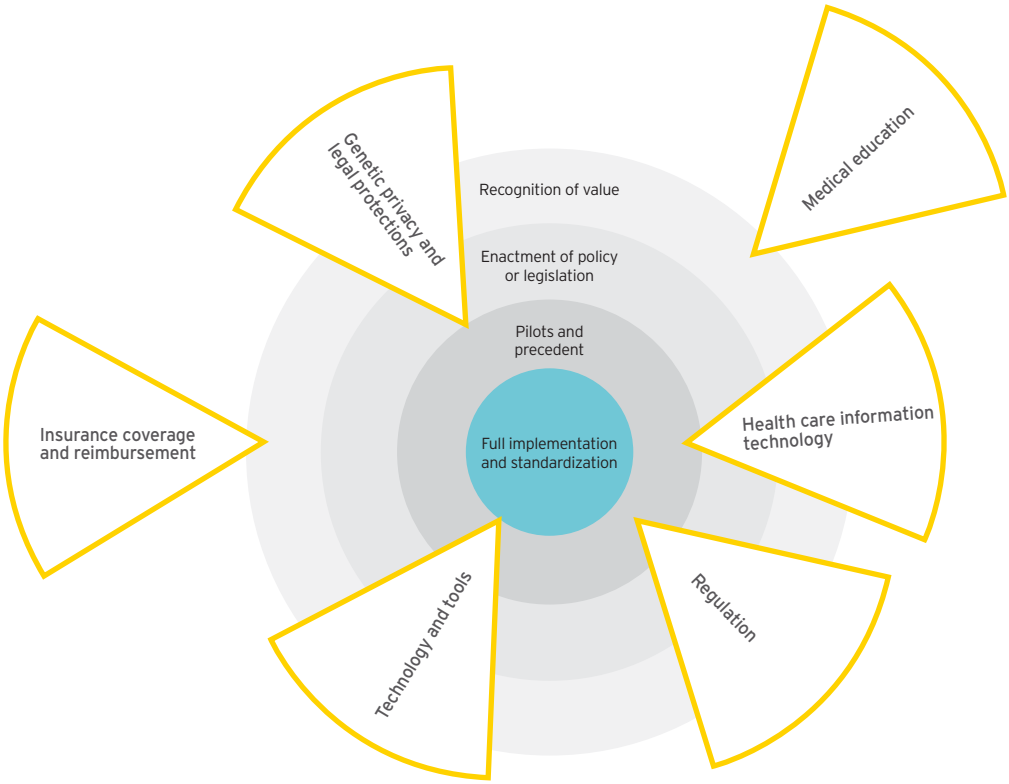
No one challenges the essential premise of personalized medicine – to deliver better therapies to patients. Made possible by the dramatic and continuing advances of 21st-century science and technology, personalized medicine can increase efficacy, decrease risk, open opportunities to prevent disease before it occurs, and lower systemic cost. Nevertheless, despite this great promise, as the chart below illustrates, we are nowhere near redefining the way medicine is practiced, even where the products that would allow us to do so are available. Indeed, there are many barriers and obstacles that deter investment in and slow the clinical adoption of personalized medicine.

In partnership with Ernst & Young, we asked seven leaders from across the health care spectrum – from a venture capitalist to a patient advocate – to suggest one change they would make to accelerate the development and clinical adoption of personalized medicine.

Taken together, their comments are revealing. They point toward a new definition for health care reform, focusing on aligning incentives in research, insurance coverage and reimbursement, and on regulation as the agents of change. If, as proponents of personalized medicine argue, the government's signals to both public and private sectors were coordinated and targeted toward the goal of achieving higher-quality, more-efficient medicine at lower systemic costs, then patients and society could both be winners.

As Health and Human Services Secretary Kathleen Sebelius has written, personalized medicine "presents the opportunity of transformational change."

State of personalized medicine adoption



Source: "The Case for Personalized Medicine," Personalized Medicine Coalition, May 2009.

The implementation of personalized medicine requires a confluence of several sectors (represented by wedges).
The concentric circles represent stages of implementation for each sector, the final stage being full implementation and standardization.

"The one thing I would change is **reimbursement for diagnostics**. I have seen too many promising products fail – diagnostics that could have improved care for cancer patients, avoided biopsies and prevented unnecessary breast cancer surgeries – because of reimbursement uncertainty. Novel diagnostics or markers are vital for personalizing care, and the lack of diagnostic reimbursement based on value is the single-biggest obstacle for personalized medicine adoption. Companies and investors make significant investments – not just to commercialize new tests, but also to collect data to demonstrate the value of these products. Reimbursement uncertainty makes it difficult to earn a decent return on this larger investment."

Ken Berlin, **Rosetta Genomics Ltd.**, President and CEO

"The one thing I would focus on is **empowering patients with genetic information**. Since people metabolize drugs differently because of their genes, some drugs will work on an individual patient while others will not. Personalized medicine will gain greater adoption when consumers can know before taking a drug if it's going to work for them or if they will have adverse reactions. Individuals should be tested at birth so they can know what therapies are likely to work and how to prevent some illnesses. This will not only improve efficacy and safety, but could also lower costs as we eliminate unnecessary medical expenses and reduce side effects."

Anne Wojcicki, **23andMe,** CEO and Co-Founder

"The one thing we need to do is to **track all cancer patients** beginning at diagnosis and conduct **thorough molecular analyses** of each patient's tumor iteratively through the course of the disease. The ultimate benefit will be to stratify patients according to molecular profiles and identify optimal treatments for specific groups. With as much as 80%–85% of cancer patients diagnosed and treated in community settings, success will require reaching these patients, engaging them in longitudinal studies and incentivizing them to continue participating in the effort. With such an approach, the oncology community stands to benefit significantly from the adoption of personalized medicine."

Kathy Giusti, **Multiple Myeloma Research Foundation/Multiple Myeloma Research Consortium**, Founder and CEO

"The one thing that I would do to accelerate the development and adoption of personalized medicine is to encourage the US federal **government** to assume a **leadership** role supporting the adoption and use of personalized medicine. The federal government should create new pathways for the clearance and **approval** of advanced diagnostics. Payors, especially Medicare, should embrace advanced diagnostics through timely coverage reviews and modernized coding and **payment** systems that recognize the value of personalized diagnostics."

Brook Byers, **Kleiner Perkins Caufield & Byers**, Partner

"The one thing we need to focus on is **developing high-clinical-value diagnostics** that make a difference for individual patients. Personalized medicine holds great promise for enabling proactive health care and preventing adverse outcomes or unnecessary complications. But a key deterrent is the perception (often based on reality) that many diagnostics are of low clinical value since they do not enable specific interventions or clinical decisions that could benefit patients. This erodes physicians' confidence in diagnostics in general – including in valuable tests that deserve their mind share."

Jay Wohlgemuth, MD, **Quest Diagnostics**, Vice President for Science and Innovation

"The one thing I would do is foster a new breed of collaborative **private-public outcomes-research studies** to answer the key question that practitioners, payors and even patients need answered: what's the real value in adopting personalized medicine approaches? This research would include real-world patients and practitioners, would not necessarily rely on traditional randomized controlled clinical trials, and would seek to measure both the clinical and financial returns from using personalized medicine."

Robert Epstein, MD, **Medco**, Chief Medical Officer

"The one thing we need to change is to better **align incentives** to enable all interested stakeholders – including drug and diagnostic companies, regulators, policy-makers and payors – to collaborate using a common language toward a common goal. Translating emerging genomic science into personalized medicine is a complex task, and we need incentives that measure and reward interventions based on their efficacy, efficiency and safety. "

Steven D. Averbuch, MD, **Bristol-Myers Squibb**, Vice President, Oncology Transition Strategy & Development and Head, Pharmacodiagnostics

Roundtable on biofuels

Embracing the future

Moderated by:
Gil Forer
Ernst & Young LLP
Global Director, Cleantech

Mark Bandak
Blackstone Advisory Partners
Managing Director

Olivier Mace
BP Biofuels
Head of Strategy & Regulatory Affairs

Bill Haywood
LS9
CEO

William Roe
Coskata
President and CEO

One of the most dynamic applications of biotechnology today is the production of fuels from renewable biological sources, known as biofuels. A host of factors are propelling biofuels development — rapid population growth around the world, burgeoning middle classes with increased purchasing power in emerging economies such as China and India, energy security concerns and the effort to combat climate change. These factors point to a growth in global energy demand and the need for a suite of new, clean energy sources such as biofuels to meet it. To gain a perspective on the current direction and outlook for biofuels, Ernst & Young convened a panel of industry participants representing an emerging innovative biofuel producer, a large energy company and leading biofuel investors to offer their views.

Forer: What are the critical components in managing the supply of sustainable alternative fuels?

Haywood: I think there are a couple of critical points in managing the supply chain. The idea is not to have to spend a lot of money on infrastructure for new fuels. In other words, we're making fuels that exist today, such as clean diesels that do not require expensive modifications to product delivery systems or engines. Because of some of the breakthroughs in synthetic biology, we can actually control the product make very closely. That is, you can dial in the exact product you want to make, and there's very little waste. So you couple minimal infrastructure changes with low-cost production, and you truly have a game-changing technology. You also have a lot of renewable feedstock in the form of sugar cane today that is not a "food for fuel" issue. When the technology to convert biomass to sugar has the correct economics, it will really open up the available feedstock opportunities.

Some of the innovation breakthroughs have taken place in fatty acid biosynthesis, which has been going on in E. coli bacteria for billions of years. So they're really at the top of the evolutionary food chain. Our ability to manipulate energy pathways in E. coli has been enabled by new equipment that's been developed — the analytical equipment to do extremely high throughput strain analysis robotically represents a huge breakthrough, especially combined with incredible computing power — now you can look at 5,000 to 10,000 different combinations overnight. It used to take months to do that. Now you can zero in much more quickly on the characteristics that you're looking for, and then you splice those together using recombinant genetics and various other synthetic biology processes.

So those are the real breakthroughs in innovation that have, at least in the biofuel arena, enabled our approach to making commercial quantities of both fuels and chemicals. These second-generation biofuels are differentiated from first-generation biofuels because they have evolved to be very high-energy molecules matching existing clean petroleum products. We focus on diesel particularly because our technology works better for more energy-dense molecules, and replacements for gasoline already exist. I think the oil and gas industry has done a great job reformulating fuels. The last frontier is to take the greenhouse gases out

of the manufacturing process. And that's what we do: take 85% of the greenhouse gases out by making these fuels from renewable resources that don't compete with food.

And, you know, in our case, sugar cane works beautifully as a feedstock just as it does for ethanol. Ultimately, this technology will be able to be run on the cellulosic sugars that are created when you can break biomass down and get the sugars out. There are many companies working on that. Once those sugars are available at cost-effective volume, we can use products other than cane juice and sweet sorghum. Our technology is feedstock-agnostic and any source of sugar works.

Roe: There are really several critical components that eventually become different verticals within this industry. I think the obvious one is the feedstock materials that would be converted into fuels. There would also be the actual conversion technologies now emerging that would facilitate the conversion. You then have the owner/operator group, which may be separate and distinct from the other two. Finally, there will be the end-fuel marketers who are actually putting this fuel into the marketplace.

Since this is still an early venture at this particular point in time, the evolution of these will occur somewhat piecemeal, but there would be certain advantages, obviously, in some sort of integration of these aspects. We believe there will be a shift in the overall value chain over time, along with who can extract the most value at different points in time.

So ultimately, I think in a more mature market, most of the value, not surprisingly, should accrue to those who control the feedstock. That's the way most of these types of commodity materials will work. But in the interim and in the early going, it will be possible to have value acquisition and value capture in separate parts of these verticals before it becomes entirely a feedstock game.

Forer: We observe increased corporate activity in the market, and not only from the oil and gas companies. From what you have seen, what has worked in terms of partnerships? Are there any lessons learned?

Mace: Everything we do in BP biofuels, we do in partnership. And certainly what we are looking for in terms of partnerships is a response to the fact that nobody knows everything about this new industry. The biofuels industry is effectively the merging of two very old and very well-established value chains. One is the agricultural value chain and the other is the energy value chain. Therefore, I don't believe there is any operator today who can claim to have all the capabilities and all the skills and know-how to make biofuels happen on a very large scale.

So partnerships are effectively a case of merging the capabilities and finding people with complementary skills who have the same vision, the same strategic objectives as you have.

Roe: I would agree with what Ollie just said. And I would add that I think as we look over our shoulders and look at what might have worked in the current manifestation of biofuels, and as we look forward to what's likely going to be involved here, it seems as though there are really sort of four fundamental areas that have to converge and to which different players and partners can bring different strengths. It's really the convergence of people and partners who can bring together feedstock, a conversion process or technology, a distribution model into the marketplace and, fourth, and perhaps most critical at the moment, the financing that allows these other pieces to come together. In each case, in each project, in each production facility, those are the critical four pieces.

So the most effective partnerships are going to be those in which the players know their respective parts and can bring one or more of those factors together.

Bandak: There is absolute strategic rationale and logic to pursuing partnerships for the reasons just mentioned, especially financing. A partnership helps validate the technology in question. It can also help an early-stage company roll out its plans throughout the country, which is critically important.

However, both parties need to know what they're bringing to the table. And there need to be complementary strengths and weaknesses. And if you also think of a JV as a marriage, is there going to be an exit? If so, how? Who is the ultimate buyer? How do

"If it takes us 20 to 30 years to get there, we have to start now and we have to have structures in place, including innovative financing structures, that will allow this to happen."

> "I'm starting to see non-traditional pools of capital being attracted to this space. They may come from traditional parties, such as sovereign wealth and private equity funds, or potentially from infrastructure funds, but they are non-traditional in trying to mitigate some of the technology risk to the extent possible."

you resolve disputes during this process? Hence, all these aspects of governance and valuation are of paramount importance.

Haywood: I also agree that partnerships are absolutely critical. We have some great partners; our VC investors, Khosla, Flagship and Lightspeed and now Procter & Gamble and Chevron, have been very supportive. These technologies take funding and government help, just as in the field I worked in for 30 years, oil and gas, where we got a lot of help from the government — depletion allowances for risky drilling, etc. The same thing applies here. You are going to need help from government. Other partners are going to be corporate partners. But it's very important to have these partners to supplement venture capital investors.

In our case, Procter & Gamble is a collaborative partner. It is working very closely with us, in a partnership, to develop sustainable chemicals. And that's really driven by its green agenda. The company has two reasons for that. One is to reduce carbon from its feedstock. The other is to smooth out some of the economic bumps that occur from petroleum prices that you can't control. If you can come up with alternative chemicals that are sustainable and cost-effective, you're going to stabilize the price of petroleum as well. So it's really both an economic and climate change approach.

Forer: What are the adoption accelerators for biofuels? Are they different in developing markets versus developed ones?

Mace: One thing that comes to mind in responding to this question is the Brazil example and the way in which ethanol actually became a mass-market reality in Brazil several decades ago. This happened to such a point that today, some people joke that the alternative fuel in Brazil is gasoline, not ethanol, since recently the ethanol consumption surpassed gasoline for the first time in the country.

Now my perspective on it is that, first of all, there was absolutely impeccable and unerring commitment from the Brazilian government to make it happen in their pro-alcohol program. Also, I believe that, at the time, it did strike a chord with the psyche, the collective aspirations of the Brazilian people in terms of how it was addressing some of the needs and desires of the nation.

I think that's an interesting example to look at, and maybe to compare and contrast with what is happening today both in Europe and in the United States.

As I mentioned earlier, creating demand, creating a market, is key in the early years — effectively kick-starting an industry by creating a market. I don't think, however, that this should be anything more than an "accelerator." In other words, I don't believe that incentives or mandates or other regulatory mechanisms to create the market, to accelerate the adoption of biofuels, should be permanent. I believe they should be temporary, up to the point where biofuels are "grown up" in a way and compete on their own merit with the incumbents, with fossil fuels.

Haywood: I think that one of the biggest issues in making renewable fuels and sustainable chemicals is that you look at the world situation — this is a very macro approach — but I think a lot of people understand it. In many foreign countries, they do not have domestic crude supply, and their economies run on imported fuels. Hence, energy security is a critical issue for a lot of places around the world. The other example is sugar cane. If you look around the world, there are many locations closer to the equator where cane grows like a weed, and it is a very energy-dense source, much better than corn, for instance. Sugar cane is not a food and there is a lot of acreage to grow additional cane. Hence, you can make new fuels from agricultural products in the next couple of years and remove dependence on petroleum.

Brazil is a great example; they are no longer at the end of the whip on petroleum prices and that's a great stabilizing effect on any economy. So I think those are great adoption accelerators. I think the other important aspect is governments — government subsidies are very important to help enable these new technologies. They don't have to be around forever, but I think it's very important that they stay in place for the next five, six years to enable these technologies. Because as they roll out — as any technologies roll out — you have a higher cost of production. As that production runs more smoothly and you gain time with the production and scale, the costs go down. So I think subsidies are another very important adoption accelerator.

Roe: I am in agreement that sustaining and enduring government policy is a critical accelerator here, and certainly we've seen evidence of that in Brazil, without question. We can question whether or not we've seen that in the United States yet. In fact, I would posit that we have not. Thirty-five or so years after the declaration that we have to become energy independent, we still don't have an enduring energy policy in this country. Every administration, Democrat or Republican, has failed to follow through on its promises.

So I agree with Ollie in that regard. I would say further that from the standpoint of a true accelerator, independent of the molecule, independent of the fuel type, whether it's ethanol or the so-called drop-in type fuels, I think a terrific accelerator would be investment tax credits (ITCs). We've seen this in other areas of the cleantech space, the clean energy space. We've seen ITCs successfully employed in wind and solar. But we have yet to see the same mechanism employed in biofuels, and I think it would be not only an acceptable, but almost necessary early incentive. Then, I would also agree with Ollie, that these incentives ultimately have to go away again.

Forer: What are some of the solutions to scaling up biofuels?

Mace: Again, it's this notion of partnerships — recognizing complementary skills and recognizing what specific partners are good at. People who are good at developing technologies and who are at the forefront of bioscience, for example, but may not have the track record or the bench strength to really do the scaling up of their process, meeting halfway with the people who are less high-tech but have more of a track record of delivering big projects at scale consistently, who have the know-how and the processes.

Roe: I would agree with that, and I would also say that there probably is some room here for true finance innovation. I don't know if it can be actualized or if we'll ever see this in the foreseeable future, but something as novel or as new as a green bank scenario that's been proposed, for example. One of the most difficult things to do today if you're ready to go, if you're ready to get a project of size up and running or up and constructed, is just the acquisition of even conventional project debt, where lenders today are perhaps rightfully gun-shy about taking chances on big projects with first-of-a-kind technologies.

It would be a huge undertaking. It's unclear whether the climate today would be conducive to such a concept. But it would be a manifestation of what we talked about earlier in terms of the need for enduring government policy and a stake in the ground that says if it takes us 20 to 30 years to get there, we have to start now and we have to have structures in place, including innovative financing structures, that will allow this to happen.

Haywood: We've linked synthetic biology with industrial biology. When I say that, the magic is really in the synthetic part, what we do inside the host organism. But the other piece is equally important; the industrial biology actually allows you to scale up, and that's really fermentation. Fermentation is not a new science. It's been around since the Phoenicians used it to make alcohols. Thus, the technology is actually older than oil and gas refining and it's very sophisticated. The Brazilians have used it effectively to make ethanol. And also in the US, we're now making a lot of ethanol using fermentation, and I think that's one of the better technologies to be able to tap into to produce at the scale that we're talking about. We didn't invent it; we're just using it. And it's very effective. It has a history of being reliable and productive, and it goes on at pretty much ambient temperatures and pressures, so it doesn't require a lot of exotic equipment. This keeps the capital costs relatively low.

I think the other issue is on the feedstock side. That's really unlocking the technology that allows you to convert biomass to sugars. There are a lot of technologies that use sugars, as LS9 does, to create biofuels. Once you produce sugars from biomass, you now move the geographies out of just the cane areas to almost everywhere you can grow cellulosic materials. You can use switchgrass, wood chips, corn stover and waste products to create sugars. I think when that happens, it will be a huge breakthrough in terms of the scaling capabilities of a lot of these technologies.

Bandak: I'm starting to see non-traditional pools of capital being attracted to this space. They may come from traditional parties, such as sovereign wealth and private equity funds, or potentially

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from infrastructure funds, but they are non-traditional in trying to mitigate some of the technology risk to the extent possible. There will be an attempt to set up a form of project financing, at least for the first or second plant, basically to get the company on its feet, to get it up and running. Then you demonstrate to the more traditional financiers, the large-capital bank providers, that this is feasible on a large scale as you roll out your plants with a more traditional capital structure. But it's something that people are starting to look at and to really come up with creative structures because it does not really fit in your classic project finance or your classic growth equity play.

Mace: Just a reflection on private or financial investors, people who'd like to play in the sector but who don't necessarily have in-house the industrial or the technological insights. I think that for them, the technological landscape for second generation must look fairly confusing right now. They've got a number of technologies being proposed to them, some using biological routes, some using various chemical routes. And I think it must be rather daunting for those providers of funding to make up their minds right now in terms of what really works and what doesn't.

Forer: Going forward, what is the role of today's leading oil and gas corporations?

Mace: Clearly, the first role is to embrace our responsibility in terms of facing up to and meeting the challenges. And the first challenge for the energy world is energy security – where it is all going to come from. I believe we're talking about roughly doubling the amount of primary energy used in 2050 versus today. Then, of course, at the same time, it's got to be low carbon; we have to mitigate climate change. So the number one role is to be proactive and really embrace our responsibility there.

Biofuels are clearly a big part of the response and, as a matter of fact, they are among the very few credible solutions in the area of transport. So the role of oil and gas operators is to facilitate the adoption of biofuels *done well*, as I certainly would not argue that all biofuels are equal. And not only to facilitate their introduction and their acceptance, but also to bring those technologies to market because of our historically successful track record of delivering large projects – of successfully delivering large capital investments. We need to promote the technologies that we see as having the ability to be winners in the long term. We need to help in selecting them and in bringing them to market in a very material way since we are not talking about biofuels being 1% or even 5% of transport energy. Our vision is that biofuels have the potential to be between 10% and 20% of global transport fuel energy by 2030.

> "The oil and gas folks are extremely important because they have the capital and the capability to build out these new technologies. They have a lot of the capability to improve production processes. And they're used to solving problems."

Roe: I think it's interesting to look at and to watch the various points of injection, if you will, or intervention into this space by the big oil and gas companies. Invariably, without their involvement, this would be a nearly impossible task.

That said, there is a real paradigm shift here. It is very difficult for companies whose foundation is a mindset that the future production of transportation energy revolves around oil reserves to start thinking about a piece of land that in perpetuity produces a feedstock material and doesn't have a finite lifetime or life cycle. This is a real shift, and I think some of the energy companies, some of the oil and gas companies, see that differently, approach it very differently and are more or less progressive on some sort of a continuum.

But clearly, whether the paradigm shift occurs completely or not, it must occur eventually. Because ultimately, success will be very difficult to achieve as long as we have internal combustion engines and liquid transportation fuels that are part of that process, unless the current incumbent oil and gas companies are very strong participants.

Haywood: I think you're beginning to see the incumbents embrace the future. But it's important to remember that they've got their businesses to run. Recently, when demand destruction hit, they took a hit like everyone else did, particularly on the refining side. Refining has been a brutal industry to be in for the last year. But the oil and gas folks are extremely important because they have the capital and the capability to build out these new technologies. They have a lot of the capability to improve production processes. And they're used to solving problems. So I think they're going to be important from an investment perspective and also in the development of these technologies as we go forward. ►

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Gautam Jaggi, Managing Editor of the publication, directed the project, wrote or edited all of the articles and managed much of the data collection and analysis. Gautam developed several new themes and elements for this year's book, including the global introduction, and had responsibility for the entire content and the quality of the publication.

Siegfried Bialojan, Germany Biotechnology Leader, led and managed the development of the European section. His team's high-quality analysis of European data and deep understanding of the science and business trends in Europe were invaluable in producing this book.

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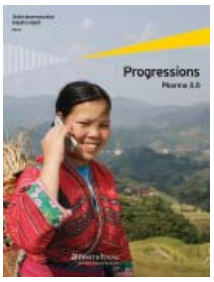

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