

25th anniversary edition

Beyond borders

Global biotechnology report 2011



To our clients and friends:

What an eventful year! Consider just a few of the biggest news stories. In a remarkable showing of people power, a series of demonstrations toppled a long-standing autocrat, while Western planes bombed another entrenched dictator, in Libya. The world was riveted by fears of radiation from a near-meltdown at a nuclear power plant. The British monarchy hosted a royal wedding that was followed eagerly by people the world over.

Sound familiar? We're not talking about 2011, but 1986 – the year our first biotechnology report was published. Indeed, many of this year's noteworthy events echo those from 25 years ago (with some key differences – the revolution was in the Philippines rather than Egypt, the nuclear accident was in Chernobyl rather than Japan, and the British royal groom was Prince Andrew rather than Prince William). That may be fitting, since biotechnology is an industry where certain themes repeat themselves with unerring regularity. Over the last 25 years, our reports have chronicled concerns and challenges – constrained venture capital, cool public markets, fears that future generations of companies might not be able to go the distance – that are still relevant today.

But biotechnology is also an industry that has seen tremendous dynamism and remarkable change. Significant numbers of companies have bucked the odds and made the journey to sustainability. The industry has brought scores of life-saving drugs to market, from targeted therapeutics for cancer to pioneering treatments for rare diseases. And looking ahead, as health care systems the world over seek greater efficiencies and proof of outcomes, the targeted approaches that biotech companies have long used stand to be rewarded.

Perhaps it's true that in biotech, the more things change, the more they stay the same. But it's also true that the more things stay the same, the more they *need* to change. The pressures on the biotech business model have now increased to extraordinary levels, even by the standards of an industry that has long faced funding constraints – something we discuss extensively in this year's *Introduction* article.

On our report's 25th anniversary, we have also questioned whether something else that has stayed the same now needs to change: the report itself. When we started this series in 1986, we were

addressing a real paucity of quality, comprehensive analysis of the industry. Since then, a number of other groups have jumped in. Today, executives can get insights from numerous biotech-specific publications, websites and blogs.

We believe our data and insights remain every bit as relevant today, particularly given the tremendous changes our clients are undergoing. But in an information-overloaded and sleep-deprived world of iPads, blogs and Twitter feeds, we are revisiting the format in which we communicate those insights. While this year's report still features a lengthy, comprehensive *Introduction* article, many of the other articles have been considerably revamped. The articles analyzing the industry's performance feature more charts – and more insightful charts that dig behind the aggregate numbers. The articles are less text-heavy, and much of the text is in the form of bite-sized commentary accompanying the charts.

In the months and years ahead, we plan to keep experimenting with new ways of keeping the content fresh and relevant – including online summaries, e-reader versions, data websites and more. Check back with us at ey.com/beyondborders. We look forward to continuing the conversation.



Glen T. Giovannetti

Glen T. Giovannetti
Global Biotechnology Leader

Gautam Jaggi

Gautam Jaggi
Managing Editor, Beyond borders

Contents

Sustaining innovation: the global perspective

1 Introduction

Sustaining innovation

4 A world of change: biotech in the new normal

8 Perspectives on sustaining innovation

Something has to give

- Riccardo Braglia, Helsinn Switzerland
 - Tuan Ha-Ngoc, AVEO Pharmaceuticals
 - Dennis Purcell, Aisling Capital
 - Hans Peter Hasler, HBM BioVentures
 - Jean-Paul Clozel, Actelion Pharmaceuticals
 - David Gollaher, California Healthcare Institute
 - Karen Bernstein, BioCentury
-

14 Perspectives on core competencies

The science of business

- Kurt Von Emster, venBio, LLC
 - Karsten Henco, HS LifeSciences GmbH
 - Mark Levin, Third Rock Ventures, LLC
 - Christoph Westphal, Longwood Founders Fund
-

18 A closer look

Payer marketing: a new business model for market access

Silvia Ondategui Parra, Ernst & Young S.L.

22 A reordering is in the works

George A. Scangos, Biogen Idec

24 Boosting innovation: a scientific method

Mark Fishman, Novartis Institutes for BioMedical Research

Reaching for growth: country profiles

26 Asian investor sentiment

Snapshots from Asia

- Norman Chen, Fidelity Growth Partners Asia
 - Utkarsh Palnitkar, Pluripotent Capital
 - Yoshihiro Ohtaki, Biofrontier Partners
 - Geoff Brooke, GBS Ventures
-

28 China: laying the foundation for innovation

30 India: exploring new opportunities

32 Brazil: fueling growth with investments and reform

33 Japan: overcoming hurdles

34 New Zealand: seeking sustainability

35 Singapore: biotech destination

Turning the corner: industry performance

37 Financial performance

Turning the corner

- United States
 - Europe
 - Canada
 - Australia
-

46 A closer look

New reporting requirements for payments to health care professionals

Diana Hoff, Ernst & Young LLP

47 A closer look

VAT and customs – a hidden cost in global clinical trials

Howard W. Lambert, Ernst & Young LLP

54 A rare focus: the legacy of a pioneer

56 Financing

Increased concentration

- United States
 - Europe
 - Canada
 - Australia
-

66 A closer look

Corporate venture capital in Europe

Siegfried Bialojan, Ernst & Young GmbH Wirtschaftsprüfungsgesellschaft

72 Project financing: from strategy to implementation

Axel Polack, TVM Capital

73 Deals

Addressing risk: options and earn-outs

- United States
 - Europe
 - Canada
 - Australia
-

77 A closer look

CVRs close the gap

Jeffrey Greene, Ernst & Young LLP

84 Dealing with options

Kevin Buchi, Cephalon

85 Products and pipeline

Adaptive strategies

- United States
 - Europe
-

93 Acknowledgments

94 Data exhibit index

96 Global biotechnology contacts



Sustaining innovation

The global perspective

vel

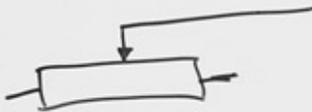
and uncertainties

$$\frac{T^2}{R^3} = \text{Constant}$$

$$F = G \frac{M_1 M_2}{r^2}$$

$$\frac{\Delta b}{b} + \frac{\Delta c}{c}$$

potentiometer



heating element



Topic 2

at
v
t

$$+ \frac{1}{2} c$$

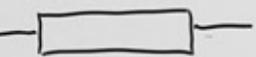
$$+ 2 c$$

- Quantum Physics
and nuclear physics

S: dis
t: +

Option D - Biomedical Ph

resistor



$$\beta = 10 \log \frac{I}{I_0} \text{ where } A_c$$

$$I = I_0 e^{-\mu x}$$

$$x_{1/2} = \frac{\ln 2}{\mu}$$

voltmeter



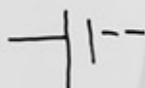
transf



switch



batt



Fv
45
11

Sustaining innovation

Given the all-encompassing nature of the global financial crisis – and the capital-intensive character of drug R&D – it is not surprising that the last two issues of *Beyond borders* dwelt extensively on the downturn and the pressure it placed on biotech's business model. In our *Introduction* articles, as well as throughout much of the reports, we catalogued the measures companies were taking and highlighted new approaches and models that were already starting to emerge – from project-based venture funding to fail-fast R&D programs to increasingly virtual organizations. And we also raised concerns about the impact on the industry's business model, as the crisis took a severe toll on funding (the model's key input) and placed innovation (its key output) under growing strain.

As we write this year's *Introduction* article – the third since the crisis hit in the fall of 2008 – the global economy is clearly on the mend. Across most of the West, GDP has been growing steadily though job growth in many countries has not been as robust. Stock markets have roared back (an occasional flash crash notwithstanding) from the depths they plummeted to in late 2008, no doubt benefitting from the efforts of central bankers to keep interest rates low. Venture capital funding has rebounded somewhat, growing by 20% during 2010 in the US alone, where the superheated interest in funding social media and Web 2.0 companies has even led to concerns about whether we may be fueling another dot-com bubble. And emerging markets such as China and India, where the crisis barely registered a blip in the first place, continue to grow at a brisk pace.

Something has to give

However, as we survey the biotech industry a year later, it is clear that the pressures on the industry's business model have only increased.

The business model: funding

Let's start by looking at funding – the key input of the biotech business model. The overall numbers look impressive. Across the US, Europe and Canada, biotech companies raised US\$25 billion in 2010 – more or less on par with the average raised during the "easy money" era of the four years preceding the crisis. But as we pointed out last year, biotech is an industry of haves and have-nots, and the real story lies in the distribution of those funds. Indeed, more detailed analysis reveals some troubling indicators. The 20% of US companies that were most successful in raising funds garnered 82.6% of capital in 2010 – up from 78.5% the previous year and 68.7% in 2005. Conversely, the bottom 20% of companies raised only 0.4% of funds – down from 0.6% in 2009.

Even as overall funding amounts held up nicely, a growing share of the total was in the form of large debt financings by mature, profitable companies. In the US alone, such financings accounted for a whopping 45% of the total in 2010 – an increase of close to 150% over 2009. In many cases, low interest rates prompted cash-flow-positive companies to increase debt on their balance sheets and use the proceeds for activities such as share repurchases and even – in a first for the biotech industry – dividends. But while balance sheet restructuring and debt optimization may be worthwhile means for large companies to maximize shareholder value, they have very little to

do with the question of how the financial crisis has affected the ability of emerging companies to fund innovation. What is most relevant for our analysis is what may be termed "innovation capital" – total funding minus large debt financings by mature, profitable companies. And on this front, the trend is exactly the opposite of the overall numbers. While total US capital raised increased by 15% in 2010, innovation capital actually *declined* by 20% over the same period.

Meanwhile, another trend – which has compounded the funding challenges faced by companies – is not even picked up in the numbers. It has become increasingly clear from interactions with investors and companies that more and more venture funding is tranced – particularly in early rounds. In the past, a company raising US\$20 million in a venture round may have received that money up front; today, it may receive only a small fraction of that total on day one – with the remainder to come only when defined milestones have been met. At the same time, we have found that press releases and other public disclosures typically reveal nothing about whether a round is tranced. So, while it is impossible to know exactly how prevalent the practice is, it is clear that even the 20% decline in innovation funding understates the extent of capital scarcity in the industry. The amount of money truly available to companies is even lower.

The widespread use of contingency-based payments may be relatively new in venture funding, but it has long been commonplace in strategic alliances, so much so that the industry even has a term for it: biobucks. When it comes to alliances, however, most press releases do disclose the amount of funding that is up-front (even as the headlines proudly trumpet total potential

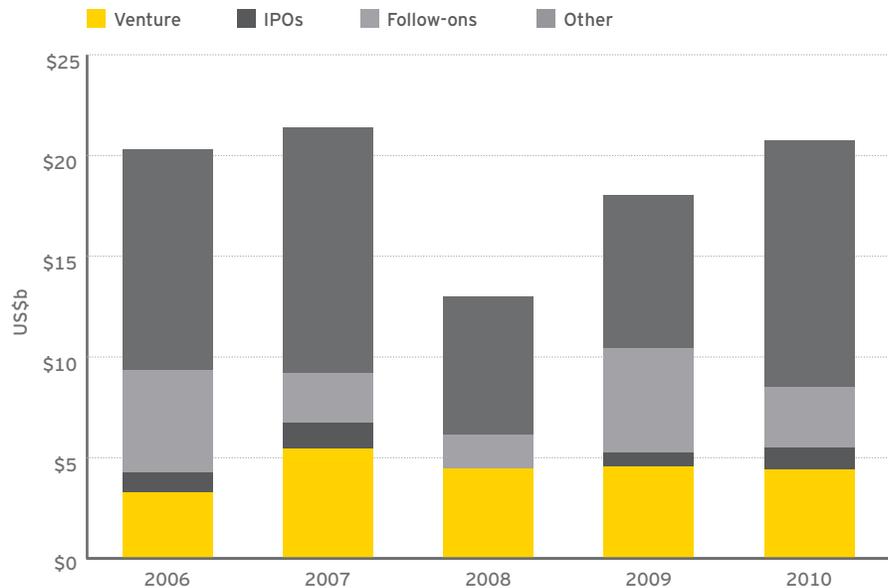
deal value), which makes it possible to analyze the trend in up-front payments. Unfortunately, our analysis shows that the trend is on a downward trajectory. For instance, in significant deals involving US or European biotech (those with a total biobucks value of US\$500 million or more), the average biobucks value has held relatively steady over the last five years, while the average up-front payment has declined by 55% over that period – falling by 38% between 2009 and 2010 alone.

Of course, there are good reasons for the use of milestone-based payments. It creates a greater incentive for biotech companies to maintain focus on critical milestones. It permits large and small companies to share more of the risk in strategic alliances. And it allows venture capitalists to improve return on investment by delaying the timing of capital calls from their limited partners. But, carried too far, the “drip feeding” of capital can have negative consequences, for instance, by increasing the incentive for biotech firms to cut corners in their R&D efforts in order to reach the next milestone as quickly as possible.

The bottom line in all of this is that investors are willing to provide funding, but it is being doled out in smaller increments and it comes with more strings attached and more risk “sharing” (which typically means that more of the risk ends up being borne by smaller biotech companies).

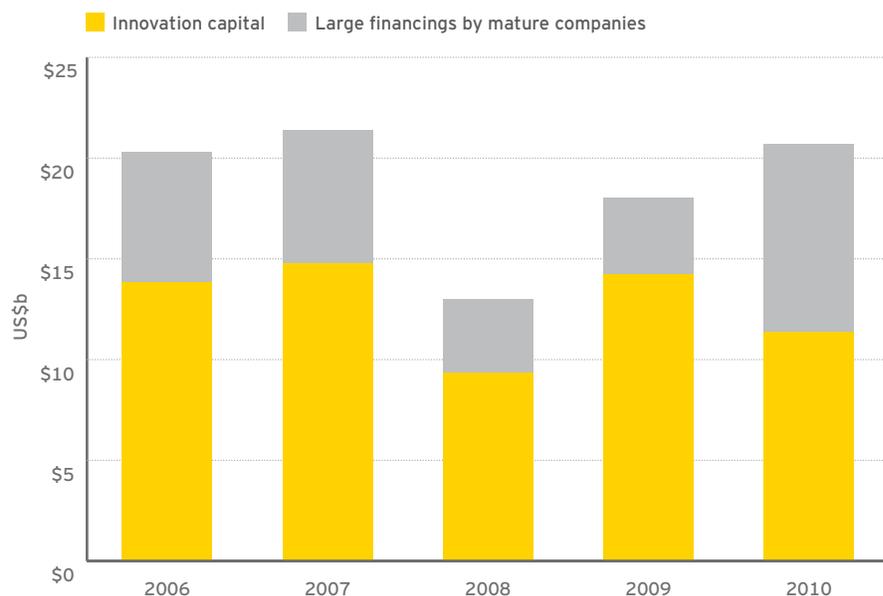
The biotech industry has also benefited historically from a healthy IPO market, which has allowed many companies to continue to fund innovation to a value-inflection point. Today, the public markets are much more challenging, with higher regulatory requirements in the US (the largest biotech sector) and a field of investors that is more selective. While the IPO market rebounded in 2010 in number

Total US funding has rebounded after the downturn ...



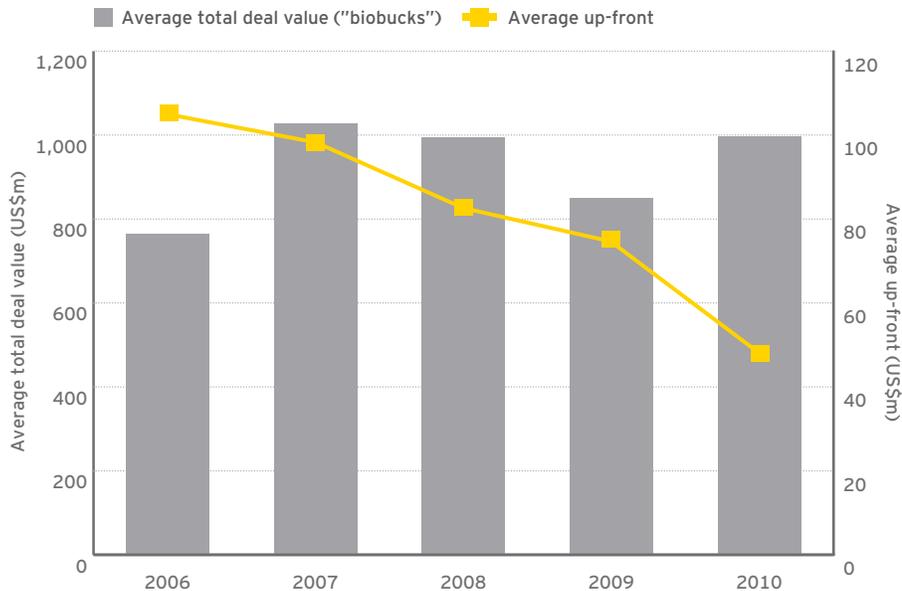
Source: Ernst & Young, BioCentury and VentureSource

... but a growing share has gone to mature, profitable companies



Source: Ernst & Young, BioCentury and VentureSource

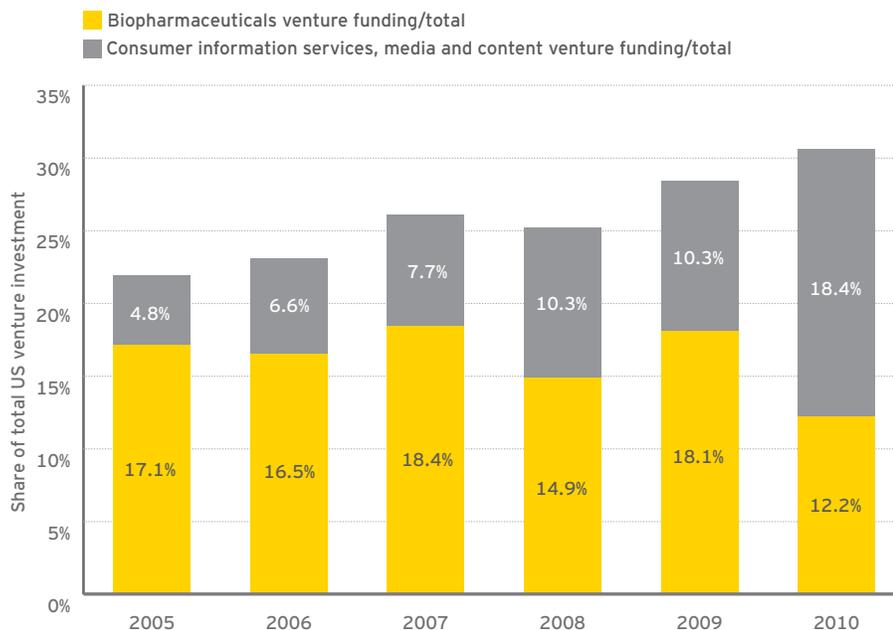
A growing gap: up-front payments have declined steadily in recent years



Source: Ernst & Young, Windhover Information, MedTRACK, BioWorld and company news via NewsAnalyzer
Chart shows data for alliances with total potential value in excess of US\$500 million.

More web, less MD?

Biotech's share of venture funding shrank as Web 2.0 investments heated up

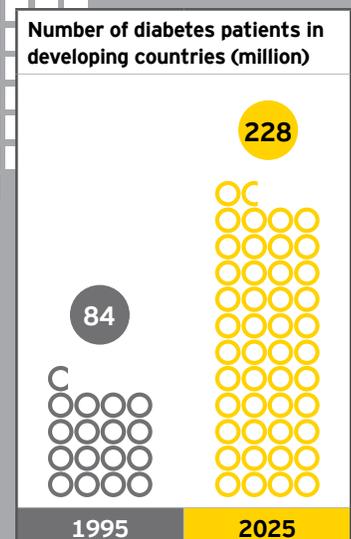
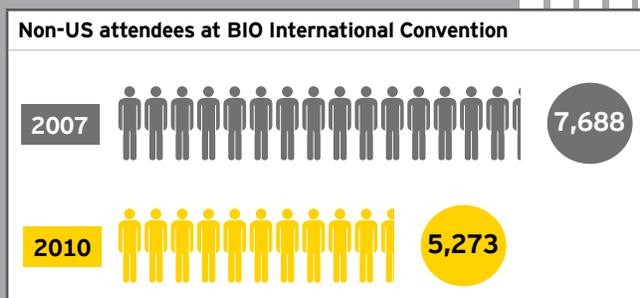
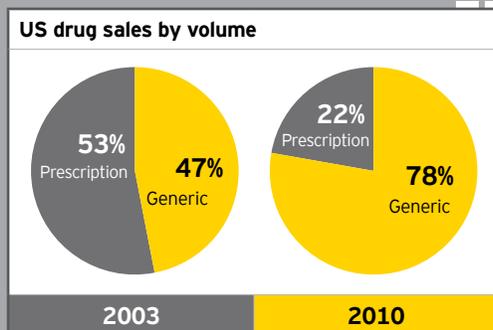
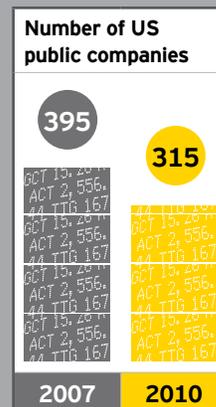
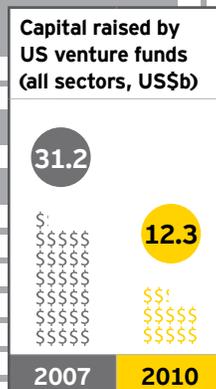
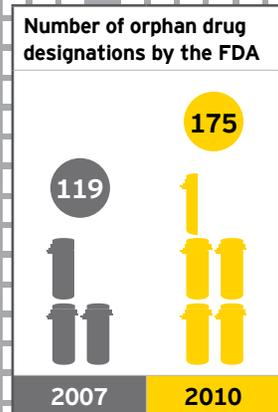
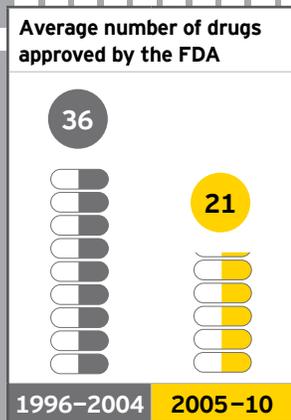


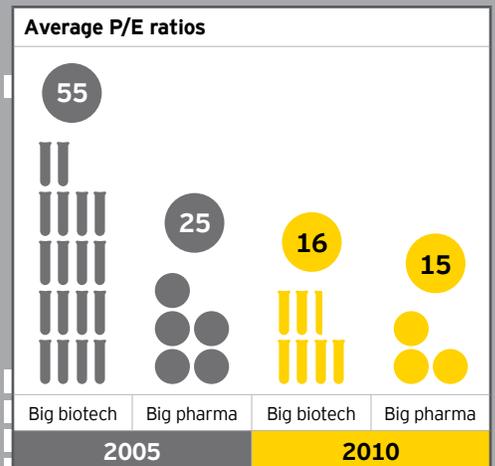
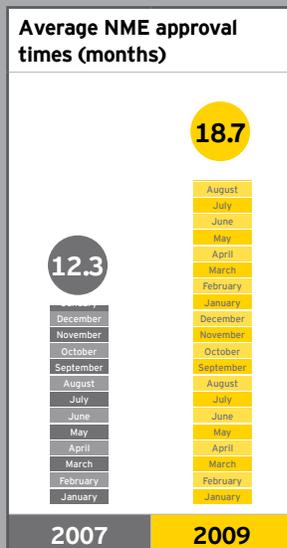
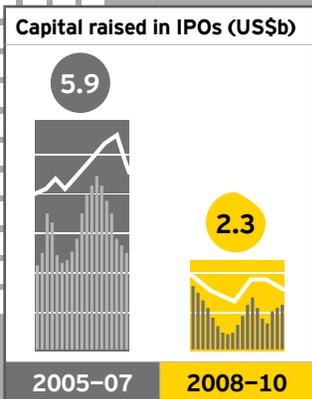
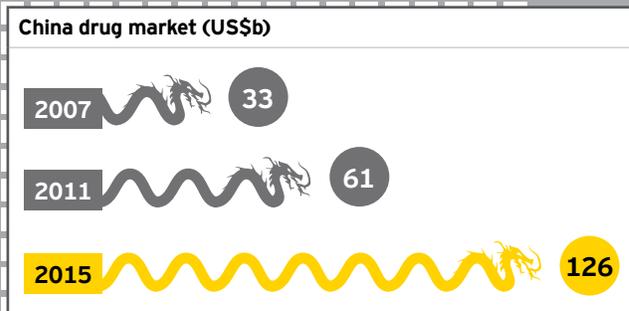
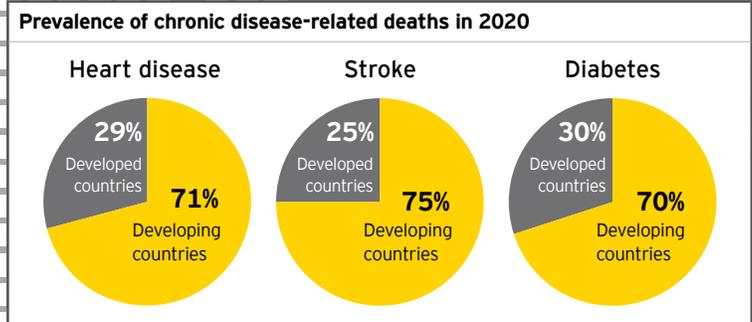
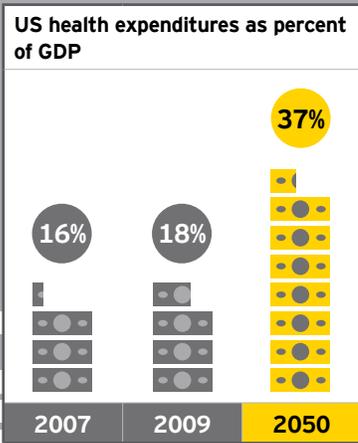
Source: Ernst & Young, VentureSource
Chart is based on US venture investments.

of transactions and aggregate proceeds, the IPO funding option (it is no longer an “exit”) is available for only a few select companies. The “windows” of the industry’s early years – typically fueled by rampant investor enthusiasm – are a thing of the past.

Meanwhile, several longer-term challenges lie ahead. For instance, while overall venture funding levels have held up so far (albeit with increased tranching), the amount of money flowing into US funds from limited partners has been declining steadily since the onset of the crisis. Data from the National Venture Capital Association show that the amount raised by US funds (across all sectors) decreased by 25% in 2010 – the third year of decline in a row. Even as less money flows into venture funds across all sectors, biotech faces increasing competition from other sectors. In particular, a lot of money has been flowing into some segments of tech and media as interest in “Web 2.0” investments has heated up, and there is even evidence that this might be starting to crowd out biotech investments. The interest in Web 2.0 companies propelled investments in consumer information services, media and content from 10% of total US venture funding in 2009 to 18% in 2010. Over the same period, biotech’s share of the total shrank from 18% to 12%. In addition, biotech faces competition for funds from cleantech, a sector that was nowhere on venture capitalists’ radar a decade ago. Further, with populations aging (among other things, 2010 was the year that the baby boomer generation started to reach retirement age in the US), large amounts of assets under management might be reallocated from higher-risk “growth” categories to relatively safer “income” investments.

A world of change: biotech in the new normal





The business model: innovation

Unfortunately, even as companies have less capital available to them, they are being called on to do more with those diminished resources as the process of discovering and developing drugs becomes increasingly lengthy, expensive and risky. This is partly being driven by the science itself. Many have pointed out, for instance, that the “low-hanging fruit” may have been plucked, and today’s scientific challenges are consequently more complex than those involved in developing earlier generations of biotech technologies and products.

In some ways, this is similar to the scientific challenge now facing an undertaking often compared to drug R&D: oil exploration (both endeavors involve expensive and high-risk bets in areas of tremendous uncertainty.) It is now generally accepted that the “easy oil” has largely been discovered, and reaching the planet’s remaining reserves will be far more challenging.

Like all analogies, the similarities only go so far. While oil is a limited, non-replenishable resource, the supply of innovative medicines should be potentially limitless. And a significant part of the cost

and risk associated with drug R&D stems from the regulatory process, since securing marketing approval requires companies to demonstrate the safety and efficacy of their products. Certainly, these regulatory requirements are there for good reason – protecting patients’ health. But the reality is that drug regulation has always involved a fine balance between a system that is too permissive (thereby putting patients’ lives at risk through unsafe and ineffective products) and one that is too restrictive (endangering patients’ lives by failing to approve effective new products in a timely manner). The concern is that the proverbial



pendulum has swung too far toward caution since the Vioxx recall of 2004. Indeed, the number of FDA drug approvals has declined markedly, from an average of 36 per year between 1994 and 2004 to an average of 21 per year since 2005 (see chart on page 86). Companies face an increasingly opaque regulatory environment, and it has become more and more common for the FDA to change its requirements regarding the data needed for approval after a company has already undertaken clinical studies – forcing companies to spend more time and scarce resources on additional data. The uncertainty created by this trend is already starting to dampen investment in the sector – particularly in disease segments where large clinical studies are necessary. It is striking, for instance, that little seed and first-round venture capital is going to companies focused on diabetes or cardiovascular conditions, despite the expectation that medical needs in these disease segments will escalate dramatically with aging populations and growing prosperity in emerging markets. (See chart on page 59.)

Even as the finish line for regulatory approval is being moved farther out, companies face more uncertainty around securing payment for their products. With health care costs outpacing inflation and budgets under pressure at a time of fiscal constraints, the imperative to make health care costs sustainable is becoming increasingly urgent. This is playing out in several ways, from legislative efforts to reform health care in major markets to outcomes-based pricing agreements between drug manufacturers and payers (see table on page 87 for examples) to the use of comparative effectiveness research in coverage decisions.

Underlying the byzantine public policy debates on health care reform are two

trends that are fundamentally at odds with each other: payers need to contain health care costs that are outpacing inflation (bending the cost curve) even as they expand access to ever-larger portions of the population. To do both at once, they will inevitably focus more and more on outcomes – evidence of how effective a medical intervention is relative to other interventions and/or to cost. For drug companies and investors, this points to a future in which they will face even more downward pressure on prices and demands that they demonstrate the comparative effectiveness and efficiency of their products. This will require more data and increase development costs. More broadly, these trends are part of the shift to an outcomes-focused health care system – something that is discussed more fully later in this article.

All of this points to an environment where sustaining innovation at historical levels is becoming increasingly challenging, as the biotech business model is under growing pressure on both ends. To sustain innovation, it is ever more clear that something has to give.

Sustaining innovation

So how can innovation be sustained? That's the question we posed to seven industry veterans – CEOs, investors and others – from the US and Europe. While their responses represent a wide spectrum of ideas (see pages 8 and 9), much of what they said can be grouped into two main approaches: prove it or lose it (i.e., pursue therapeutic areas and strategies to demonstrate how you are improving outcomes) and do more with less (i.e., boost operating efficiency).

Indeed, these are imperatives that arguably confront *all* companies in the life sciences industry. In the past, we have referred to biotech and big pharma as “one industry divided by two sets of challenges,” and the concerns facing the two segments were frequently mirror images of each other. Biotech companies were often brimming with innovative new technologies and product candidates but short on capital, while big pharma companies have been relatively flush with cash but hungry for assets with which to replenish their pipelines. While the same challenges continue to face both segments today, we are increasingly moving toward a world in which all life sciences firms will need to operate more efficiently even as they dedicate more resources to demonstrating value.

Of course, there are some key differences. For instance, big pharma companies' drive for operating efficiencies – manifested in megamergers, restructuring initiatives and layoffs – is motivated by the fact that many of their biggest cash cows are going off patent and their R&D efforts have not been productive enough to plug the ensuing gap. For emerging biotech companies, on the other hand, the need for efficiency stems from an entirely different source – the tight funding environment that has followed the global financial crisis and economic downturn.

The following discussion examines how these two imperatives – “prove it or lose it” and “do more with less” – are affecting biotech companies, and how creative approaches to both challenges will be key to sustaining innovation in the future.

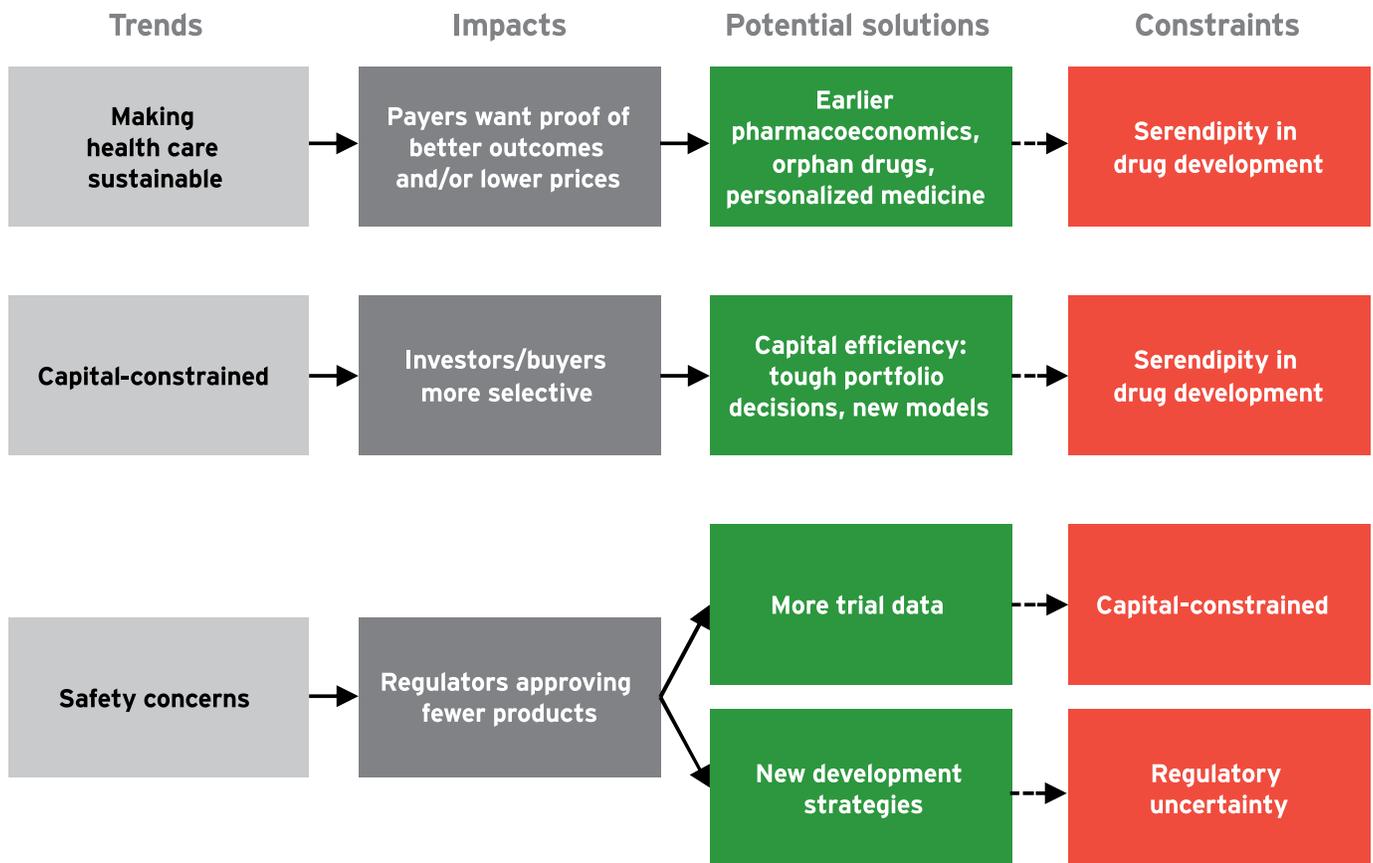
continued on page 10

Something has to give

The life sciences innovation model is under strain on multiple fronts, and the challenging business climate is constraining the viability of potential solutions. As the need to make health care sustainable becomes more urgent, payers are demanding evidence of better outcomes while squeezing prices. In response, companies are adopting earlier pharmacoeconomic analyses and more targeted approaches. Similarly, firms are responding to a constrained capital environment and increased investor selectivity with capital-efficient approaches to R&D. But in both cases, the serendipity of drug development raises the risk of

losing innovative breakthroughs. On the regulatory front, a risk-averse FDA is forcing companies to develop more data, but capital constraints make it increasingly difficult for companies to conduct the trials needed. And while new development strategies could provide potential solutions, regulatory uncertainty is making it more difficult for companies to use such approaches.

In short, there are few easy answers. So we challenged seven industry leaders to give us their views. What needs to change to sustain innovation? How will that change happen?



Focus on the science

Today, regulatory authorities are making the approval process more complex, while payers are squeezing returns and shortening the time frame for payback. Addressing these pressures – e.g., through longer patent exclusivity or more realistic approaches to product safety – would make innovation more sustainable. But even without such changes, we can sustain innovation by going back to the science. This means focusing on clinical relevance rather than making regulatory requirements and payers' demands our main obsession. We are here to meet unmet medical needs, and innovations that do that will always get approved and paid for.

Riccardo Braglia, CEO, Helsinn Switzerland

Target drug development

Innovation has been hampered by the extremely high cost of developing new oncology drugs compared to the low probability of clinical success. To sustain innovation, we must contain costs while simultaneously providing the maximum clinical benefit to patients. This requires targeting drug development efforts to patient populations most likely to benefit from specific therapies – precisely the approach we are using at AVEO.

Tuan Ha-Ngoc, President and CEO, AVEO Pharmaceuticals

Be patient-centric

Historically, drug development companies have focused on preclinical assays, clinical development pathways and FDA interactions. Although the patient has always been the light at the end of the tunnel, companies have been slow to obtain patient input early in the development process. Looking ahead, as patients increasingly act as consumers that weigh prescription co-pay costs against a therapy's efficacy/safety, companies need to involve patients and patient advocacy groups earlier. Not only can these groups help speed clinical trial enrollment and FDA interactions, but they also allow companies to gain early assessments of the ultimate commercial prospects for new therapies.

Dennis Purcell, Senior Managing Partner, Aisling Capital

Partner early – when needed

For small biotechs, venture funding is becoming more difficult and public markets less receptive. While deal-making with pharma is still strong, staged deals often give biotechs most of the risk and little initial reward. In niche/orphan indications, therefore, small biotechs should be prepared to go all the way to approval – though this obviously requires strong financial backing. In large (blockbuster) indications, companies need to find partners early on (preclinical or after Phase I), since there is significant risk of getting stuck after Phase II, even with positive data. In short, if you can't make it all the way, partner early.

Hans Peter Hasler, Chairman, HBM BioVentures

Change structures and cultures

If we are to sustain innovation at past levels, we will need to make changes that are both structural and cultural. Most biotechnology companies today are not organized and do not have the right culture for dealing with innovation. Small biotech companies often have the same organizational structures and processes as their larger counterparts. This needs to change. I believe there will be a Darwinian natural selection process, and only biotech companies that are willing and able to adapt to the needs of innovation will survive.

Jean-Paul Clozel, MD, CEO, Actelion Pharmaceuticals

Revamp the FDA

We don't ordinarily think of FDA regulation as industrial policy, but for biotech it is. The agency has effectively discouraged investment – whether by large companies or VCs – in whole fields, from obesity to diabetes to cardiovascular disease. As a result, innovation is migrating to Europe and Asia. To reverse this trend, policy makers first need to grasp the FDA's pivotal role in US competitiveness and job creation. Then they need to press the agency to improve its performance in ways that make launching new products in the US at least as straightforward as launching them in Europe.

David Gollaher, PhD, President & CEO, California Healthcare Institute

Redesign clinical trials

Innovation is *not* at risk – though people who cannot innovate definitely are. Smart money is still funding innovation – selectively, as it should. Individuals and institutions are developing potential solutions: better disease models, new funding models for translational research, solutions for payer demands. Many complaints would go away if we could fix the one place where managers and investors have no control: the regulatory system. Everyone would be better off if we ditched the rigid Phase I-II-III-approval model and went to more adaptive trials and conditional approvals with large patient registries to collect robust safety and efficacy data.

Karen Bernstein, PhD, Chairman, BioCentury



Drug companies will need to fundamentally change their mindset and approach from “if you develop it, the system will pay” to “prove it or lose it.”

Prove it or lose it

The health care industry is in the early stages of a sweeping transformation: the movement to an outcomes-driven ecosystem. Readers of *Progressions*, our sister publication for the pharmaceutical industry, are aware that our last two annual issues have focused almost exclusively on this trend. In those reports, we emphasized the implications for large commercial-stage companies. But the focus on demonstrating outcomes does not affect large organizations alone. Indeed, thinking about outcomes will increasingly affect *all* companies in the health care arena and will permeate almost everything they do.

The shift is being driven by the simultaneous occurrence of two key drivers: the need to make health care sustainable (discussed above) and the coming of age of new technologies (e.g., m-health, e-health, digital health records and social media). These technologies are enabling new solutions that have the potential to make health care more sustainable, while the growing urgency of the sustainability issue is accelerating adoption.

At its essence, this is about changing behaviors. As the need to make health care sustainable becomes more acute, payers will inevitably need to pay for the products, services and solutions that are most effective and stop reimbursing the ones that don't work as well – which will spur fundamental behavioral changes by actors across the health care ecosystem. Providers will need to change their behaviors by measuring the effectiveness of different interventions and develop best practices based on evidence rather than habit or conventional wisdom. Patients will need to change behaviors as they are increasingly incentivized by health care reform – and

also empowered by new technologies that democratize information and make it more transparent – to focus on prevention, manage their health and behave as the “superconsumers” of tomorrow rather than the passive patients of yesterday. And drug companies will need to fundamentally change their mindset and approach from “if you develop it, the system will pay” to “prove it or lose it.”

In a prove-it-or-lose-it world, the fortunes of a drug company are not determined just by the number of doses it sells, but rather by how well it can demonstrate that its product is improving health outcomes – an essentially different proposition. Proving it to regulators will likely involve crossing a higher bar – not just demonstrating that a product meets a *de minimus* standard of safety and efficacy, but also that it is truly differentiated and has a strong safety and efficacy profile relative to existing treatments. Proving it to payers will require creative approaches to demonstrate the superiority of a product (e.g., pharmacoeconomics, comparative effectiveness research, data mining using digital health records) and/or take on more of the risk that a treatment may not work (e.g., outcomes-based pricing approaches). To gain acceptance, products will increasingly have to significantly improve the standard of care or be demonstratively less costly than the current standard of care.

But the prove-it-or-lose-it concept does not apply just to regulators and payers. In an environment where everyone has to do more with less, it is only natural that all of the stakeholders in the health ecosystem will be more careful about how they allocate scarce resources – and require more proof that something works before they pay for it. Indeed, many of the funding-environment changes we discussed earlier reflect this

reality. From tranching venture rounds to smaller up-fronts in alliances and contingent value rights in acquisitions, investors are requiring more proof before parting with their money. While there is little that companies can do up-front to demonstrate the efficacy of their drug candidates, demonstrating that they understand the market realities for their product and have thought about the pharmacoeconomic issues will help increase the comfort level of investors.

Do more with less

Given the basic nature of the model we described earlier – in which funding is the key input and innovation the key output – doing more with less inevitably involves some combination of using capital more efficiently and conducting R&D with greater efficiency.

Funding: the capital agenda

Ernst & Young's “capital agenda” framework provides a good lens for examining different aspects of capital efficiency. As shown in the accompanying chart, this framework organizes all of the capital-related activities of a company into four categories: raising capital, preserving capital, optimizing capital and investing capital. Historically, of course, emerging biotech companies have been most focused on one quadrant – raising capital – since their very survival has depended on it. But in today's new normal, as raising capital has become more challenging, companies will also need to pay close attention to preserving and optimizing their more limited resources.

Raising capital. As discussed earlier, raising capital has become far more difficult in the aftermath of the global financial crisis. Funding has become more skewed, with relatively less money going to finance

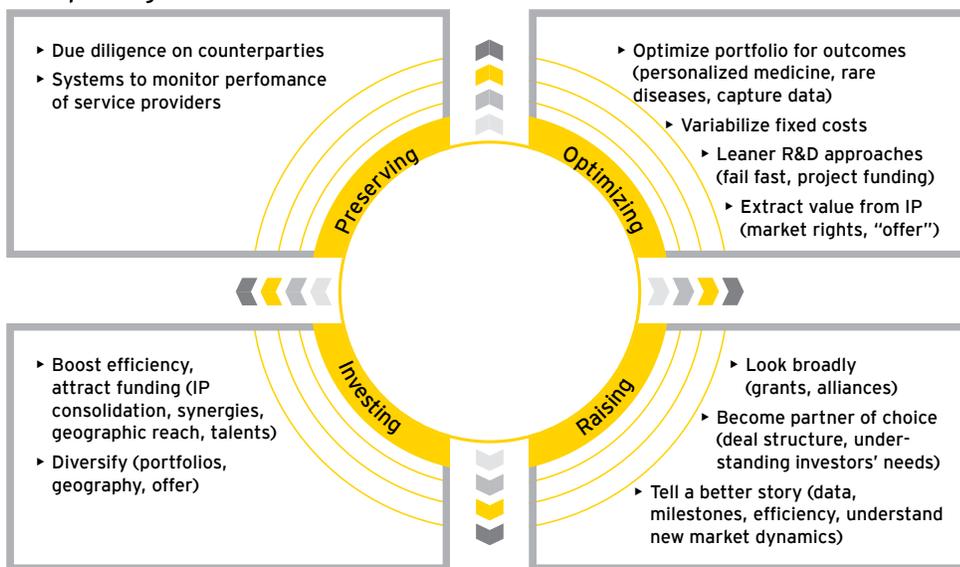


innovation at emerging companies. As a result, companies are looking more broadly for capital, tapping resources such as government funding programs and disease foundation grants. In Europe, non-traditional sources of funding, such as corporate venture capital and “family offices” (wealthy, family-controlled pools of capital), have become much more visible since the advent of the financial crisis. (For more on these trends, refer to the “Financing” article on page 56.)

The tight capital markets make it all the more important for biotech companies to focus on their other long-standing source of funding – strategic investors. To become a “partner of choice” – particularly at a time when large companies face growing pressures of their own and have more leverage at the negotiating table – emerging biotechs will need to calibrate their approaches to the needs of their potential partners. For instance, many big pharma (and indeed, big biotechs – refer to the article by George Scangos, Biogen Idec’s CEO, for one example) are restructuring their pipelines and moving out of entire disease classes that are no longer deemed strategic. Biotech companies looking for partnerships as a source of capital will need to watch this dynamic and shifting landscape closely. With a shrinking pool of potential partners, they will need to tell a different “story” – one that reflects the changing needs of their partners and the growing pressures on the regulatory and reimbursement front (more on this later). This extends to an understanding of where a particular technology fits into the potential partner’s strategy and how it may measure up against the partner’s programs – whether sourced internally or externally.

Optimizing capital. In addition to expanding and differentiating their approach to raising capital, companies need more than ever

A capital agenda for the new normal



Source: Ernst & Young

to extract more value out of their existing assets – i.e., they need to optimize capital. Since the most valuable existing asset that most emerging companies have is their intellectual property, companies are focusing more than ever on ways to extract more value from their IP. This can include tried-and-true approaches such as retaining some commercialization rights (typically by geography or disease focus) while giving others away through strategic alliances. More creative approaches could include reconsidering a company’s market offering. For most drug companies, the value of everything they know is captured and monetized through their products. But by expanding its offer (e.g., to services, diagnostics, data), a company could capture more of the value through different channels.

Capital optimization also includes more virtual approaches – e.g., outsourcing, building an “extended enterprise” of collaborators with fewer permanent employees and less real estate – that allow

firms to reduce overhead by “variabilizing” fixed costs. And since R&D is by far the biggest expenditure undertaken by emerging companies, companies and investors are increasingly looking at solutions that allow for leaner R&D, such as fail-fast and project-funding approaches. (For a detailed discussion of these models, refer to “The new normal,” the *Introduction* article in last year’s *Beyond borders*, as well as the piece by Axel Polack of TVM Capital in this year’s report.)

More than ever, capital-optimizing decisions will need to be made in light of the prove-it-or-lose-it imperative. Prioritizing pipeline assets, for instance, will increasingly be done not just based on scientific merit, but also on the likelihood that companies can assemble a compelling data package regarding the economic efficiency of the product so that payers will pay at adequate levels if it succeeds in obtaining regulatory approval. For instance, in an environment where third parties – agencies such as NICE or IOM, large providers, payers and others –



are increasingly able to analyze their data to make decisions about companies' products, it becomes important for firms to make sure they are capturing relevant data of their own to inform these decisions. Personalized medicine approaches – such as identifying a biomarker and collaborating to develop a companion diagnostic – may be more palatable for payers, since such measures are likely to differentiate a drug and make it more efficacious in a specific patient subpopulation (though this also increases the average price per patient – more on this aspect later).

Preserving capital. Preserving capital – reducing and managing risk – has become more important because many of the new approaches and models companies are experimenting with can also create new risks. For instance, as companies increase their use of outsourcing and work with virtual company models, the need for due diligence on counterparties in extended enterprise becomes more critical. To conduct this, firms will need systems to monitor the performance of service providers and other counterparties. They will also need new processes, competencies and incentives – something that is discussed more fully later in this article.

Investing capital. The fourth quadrant, investing capital, is also increasingly important in today's economic climate. While one might intuitively think of most pre-commercial biotech companies as being investees rather than investors, the business of biotech has always been as much about investing capital – in facilities, human assets, intellectual property and more – as it has been about raising funds. In the new normal, the pressure to invest scarce resources wisely and efficiently is more acute than ever.

On a selective basis, companies can consider strategic investments as a means of boosting efficiency and potentially making themselves more attractive to strategic and financial investors. This might include mergers or alliances with other companies to realize synergies, such as reducing duplicative overhead or consolidating fragmented intellectual property. Efficiencies can also be realized through deals that diversify one's focus by giving a company more potential sources of return on its investments. Examples include expansion into other diseases or geographic locations. Diversification could also mean expanding one's market offering beyond drugs – for instance, into services and solutions that could be increasingly valuable as the imperative to prove it or lose it becomes more prevalent.

R&D: targeted approaches

So far, we have been talking about prove-it-or-lose-it and do-more-with-less as two distinct imperatives. Of course, companies will have to focus on both challenges, and there may appear to be some dissonance here – even as emerging biotechs are having to contend with constrained capital and stretched R&D budgets, they are being compelled to extend those scarce resources even further to placate payers and prove the value of their products. The reality, however, is that the two challenges are converging in many ways. In an environment where value will increasingly accrue to differentiated products that can prove their worth, the most prudent use of scarce resources will be to invest in the approaches and market offerings that are best aligned with that trend. Over time, this is no longer an either/or. "Proving it" is doing more with less. You mitigate one problem by focusing on the other.

In an environment where value will increasingly accrue to differentiated products that can prove their worth, the most prudent use of scarce resources will be to invest in the approaches and market offerings that are best aligned with that trend. Over time, this is no longer an either/or. "Proving it" is doing more with less. You mitigate one problem by focusing on the other.

This is most evident, perhaps, in targeted approaches to R&D, which are located squarely in the sweet spot where the two imperatives intersect. Personalized medicine – using genetic data to target drugs to the subpopulations in which they are most likely to be effective – has existed in theory and practice for quite a long time, but it is more relevant than ever for today's market challenges. Increasing numbers of drugs have biomarkers associated with them today – measures that can "prove it" by transforming therapies from blanket shotguns into precision-guided weapons that are devastatingly more effective against the diseases they target. But these approaches can also do more with less by reducing risk and making R&D more cost-effective. With smaller patient populations, clinical trials can be smaller and cheaper, although patient recruitment can be a challenge and payers may require more post-marketing surveillance because of the small clinical trial sizes. With better identification of the patients to whom a drug should be targeted, safety issues are less of a risk. And of course, using targeted approaches can reduce the greatest risk of all – that of pipeline failures. (A more extensive discussion of the economics of personalized medicine may be found in *Beyond borders*

What we are witnessing, in other words, is a glimpse into the future of medicine. The way companies approach rare diseases today is the way they will approach all diseases in the years ahead.

2008, particularly the introduction article, “Reinvention and reinnovation,” and the roundtable on personalized medicine, “From efficacy to efficiency.”)

Against this backdrop, it is not surprising that interest in rare diseases has picked up in recent years. While orphan drug incentives have been around for well over two decades (the US Orphan Drug Act was passed in 1983, and similar laws were enacted in key markets such as Japan, Australia and the European Union in the 1990s), the area has gained much more traction in the recent past. The number of orphan drug designations by the FDA increased from 119 in 2007 to 175 in 2010. Even more striking, big pharma companies – which invented the blockbuster model and until fairly recently were focused almost completely on drugs with large markets – have enthusiastically embraced the field. Notable examples include Pfizer’s entry into Gaucher’s disease in 2009 and Sanofi’s acquisition of Genzyme in 2011.

Genzyme, of course, was a pioneer in the field, realizing that there was a viable market in rare diseases long before most other companies did. To note the company’s legacy – and given the emphasis on rare diseases in this year’s *Beyond borders* – we have a two-page spread on Genzyme’s history and approach on pages 54 and 55. As Henri Termeer, Genzyme’s outgoing CEO, notes, success in rare diseases requires concerted focus on patients. Since its earliest days, the company made it a priority to maintain a registry of its patients and build relationships with each of them. In our 2008 report, Henri offered additional insights, pointing out that “above all else, companies need to demonstrate value. We have consistently obtained reimbursement, even in the most difficult countries, because we can show that our products work, and

they have clear diagnostics to identify the right patients.”

It’s striking that, while Henri was talking about orphan diseases, his statement could just as well have been made about the growing imperative to “prove it or lose it” across *all* diseases. And that reality, in essence, is why the economics of rare diseases have become increasingly compelling in today’s industry – the approach they require is broadly applicable. As Mark Fishman of the Novartis Institutes for BioMedical Research points out in his guest article in this year’s report, NIBR focuses extensively on rare diseases and is attracted to them because “the mechanisms that underlie these diseases are usually shared by more common diseases, so understanding them can shed light on multiple ailments. So our approach is often to start by developing a drug for a rare disease and then apply it to more common ones later.”

What we are witnessing, in other words, is a glimpse into the future of medicine. The way companies approach rare diseases today is the way they will approach all diseases in the years ahead. The future is one where more and more drug development will involve targeted approaches for smaller populations. It is one where diseases will be understood and classified based on their mechanisms of action rather than the symptoms they manifest. And it is one where patient-centricity will be a cornerstone of success. We may ultimately need a new terminology as what is rare today becomes commonplace tomorrow. Some observers have even raised the possibility that the “new orphans” may be yesterday’s blockbuster indications – chronic diseases, where the incentives for developing drugs are getting squeezed as regulators demand more data about safety issues and payers demand more proof

of comparative effectiveness against the generic equivalents of proven and highly efficacious blockbuster drugs.

To sum up, the economics of the targeted-therapeutic, rare-disease approach are becoming relatively more attractive, thanks to smaller clinical trials, less generic competition and fewer safety issues. But this is no panacea for the pressures facing the industry. So far, payers have been willing to pay any price because orphan drugs have addressed medical needs that were completely unmet and because patient populations have been so small that covering these drugs has had a negligible impact on their budgets. But as more and more drug development is targeted to smaller patient populations, the economics will likely change. A high price tag may be no big deal if it applies to a very small patient population. But payers will certainly resist those prices to a greater degree once they start applying to much larger numbers of patients. Indeed, we are already starting to see this trend. In recent years, NICE has denied coverage to some of biotech’s most efficacious targeted therapies for cancer (an action that has also often generated an outcry from patients and politicians, leading to some high-profile reversals). And we are seeing more examples of payers pushing back on orphan drug prices and treating them less favorably in formularies. The bottom line, perhaps, is that rare diseases cannot expect a free pass from payers going forward. Like all drugs, they will face increased scrutiny and have to make a compelling case to justify their value. In many cases, they may no longer command the prices they have historically. But it is still absolutely true that such targeted treatments stand a better chance of securing coverage than most other drugs in the prove-it-or-lose-it future.

continued on page 16

The science of business

Multiple competencies



Kurt von Emster
venBio, LLC
Founding Partner

In today's challenging business climate, management teams need several core competencies. The first is *market awareness*. Venture-backed companies can no longer simply assume there will be funds available to pursue multiple products; they need to focus on investor returns and liquidity. Public company executives need to understand why some biotech stocks have declined for prolonged periods while others have thrived, and that focusing on efficiency has become an important value driver.

The second competency is *prudence*. With increased market awareness, leaders need to ensure that they are not overextending precious resources in inappropriate ways. If regulatory changes are likely to make drug development more challenging in a disease area where you are currently focused, your approach needs to change.

The third competency is *partnering for value*. In today's climate, you may need to partner early, which may involve sacrificing upside – particularly in a period of lower valuations. But doing so may also allow you to raise capital for secondary programs, where the best value may lie. So picking which programs to fund internally and which to partner is more important than ever. This requires weighing cost and benefit – money invested in each program for every dollar of return – instead of simply focusing on market size. The success of orphan drug approaches amply demonstrates that large markets are not everything.

Lastly, CEOs increasingly need the ability to *orchestrate virtual operations*. We've seen a dramatic rise of virtual company models in recent years. In these approaches, CEOs need to be orchestra conductors more than drivers – with strong project management, research and clinical oversight and the ability to work across different time zones and personnel orientations.

Partner early and partner often



Karsten Henco, PhD
HS LifeSciences GmbH
Managing Partner

The funding downturn in Europe has been deeper – and more prolonged – than in the US. In Germany, for instance, some family-owned firms and non-traditional investors are still active, but institutional venture capital has all but disappeared and the IPO window is tightly shut. This bleak environment has real implications for how company leaders need to operate.

In the past, CEOs focused mainly on selling their stories to financial investors. But today, with funding scarce, most companies can no longer count on raising US\$150 million through traditional channels to reach proof of concept, and so the focus needs to be on strategic buyers such as big pharma. Success, in other words, is about becoming a partner of choice for larger companies at a relatively early stage. This requires different approaches and skills. Attracting VCs or public investors required financial dexterity and relatively superficial stories. But to sell something at an early stage to the pharmaceutical industry requires building extremely convincing data packages. So a core competency of the CEO is the ability to understand how to build data packages that will be attractive to a pharma buyer – for instance, data based on clinical experience, which is very valuable these days. CEOs need to understand the structures of large companies and track changes that are taking place in their strategies and needs. This is far more difficult than selling a story to venture investors. And of course, quantitative skills in areas such as pharmacoeconomics are increasingly important.

Efficiency is the name of the game, and small companies should not waste resources doing things that established firms can do better, such as manufacturing and large clinical trials. Management teams at start-ups no longer have the luxury of learning by doing. You need experienced managers on day one.

Succeeding in biotech's challenging environment has always required a certain combination of skills and competencies – building the right team, communicating a compelling “story” to strategic and financial investors, responding opportunistically to changes in investor sentiment and delivering strong results on the R&D front. Today, management teams face new and heightened challenges, including navigating new funding and business models and dealing with the shifting definition of “success” – not just product approval but also reimbursement as payers increase their focus on differentiated health outcomes in their coverage decisions.

In this context, we interviewed four industry veterans to get their insights on how the critical competencies of biotech company CEOs and management teams are changing. **Kurt von Emster** of venBio is a seasoned Wall Street veteran and venture investor who serves on the boards of several biotech companies. **Karsten Henco** of HS LifeSciences is a serial entrepreneur, having founded or cofounded fourteen companies, including Qiagen, Evotec, U3 Pharma and Coley Pharmaceuticals. **Mark Levin** of Third Rock Ventures started his career at Lilly and Genentech before founding and serving as CEO of Tularik, Focal, Stem Cells and Millennium Pharmaceuticals. **Christoph Westphal's** career has included roles as a consultant (at McKinsey & Company), as cofounder and CEO (of Sirtris, Alnylam and Momenta) and as a venture investor (Polaris Ventures, SR One and now Longwood Founders Fund).

Flexibility and resilience



Mark Levin
Third Rock Ventures, LLC
Partner

At Third Rock, we aim to launch transformative companies in disruptive areas of science. While our hands-on internal team provides strategic guidance, it's critical to identify the right managerial talent to run these companies. For a “traditional” biotech company focused on breakthrough biologics and platforms, the primary focus is R&D – particularly in early stages. So CEOs are invariably scientists with extraordinary R&D experience and a passion for making a difference. Of course, business understanding is becoming increasingly vital. Therefore, we supplement CEOs with management teams and boards that have complementary skills in areas such as business development and operations. A year or so before entering Phase II trials, we add regulatory, clinical and commercial managers to start focusing on reimbursement and health economics.

How is the current environment changing the competency profile? Everyone is focused on efficiency, which is boosting outsourcing and virtual business models. In turn, this requires different managerial competencies around identifying where to outsource rather than build internal strengths, and it requires handling outsourcing partnerships like strategic alliances rather than mere contractual arrangements. A successful virtual approach involves building genuine teams, soliciting input and spending time at partners' sites.

Above all, leaders need flexibility and resilience in this uncertain environment. This includes solid experience, knowledge about the needs of payers and regulators, and the ability to think strategically about the downstream consequences of decisions. Otherwise, it's easy to panic and make decisions in discovery that might irreparably harm the company down the road. Indeed, while everyone is focused on efficiency in this market, the biggest cost savings may come from the opportunity cost of making the right decisions in discovery and early development. The decisions you make today can have \$100 million consequences downstream.

Business – not just cool science



Christoph Westphal, MD, PhD
Longwood Founders Fund
Partner

Since the fall of 2008, access to capital has become much more constrained. Several VCs have responded by funding leaner “projects” rather than full-fledged companies. This might seem to imply that the most important managerial attribute is the scientific and technical expertise to develop a pipeline asset from point A to point B. I would argue the opposite – that business skills are even more important now. In a capital-constrained environment, there is much less room for strategic error.

Cost efficiency is important. When we sold Sirtris Pharmaceuticals, we were 50 people, with maybe another 80 in China. Going forward, the model will shift even more to outsourced resources, which will require enhanced management skills and cultural flexibility. As more and more venture transactions are tranced, this creates a different dynamic in boardrooms. In this environment, CEOs are very focused on the next milestone, with much more oversight from the board. So being able to navigate this environment and having a strong team in place that can work collaboratively with venture investors are key.

Through most of my career, success has come from falling in love with great science. But today more than ever, building value for investors requires a deep understanding of and a healthy respect for the business climate. Does the disease segment you're focusing on already have many good treatments? Is this a well-differentiated mechanism? What will it take to commercialize this product? Do you have the resources to take it to market or to a key inflection point where you will attract handsome offers? Having strong answers to these questions can mean the difference between groundbreaking science and a breakthrough treatment that can deliver value for patients and investors.

Getting there

In this section, we discuss what it will take for companies to succeed in addressing the two imperatives discussed earlier. If the two imperatives address *what* companies need to do, this section addresses how they will need to proceed to achieve those goals.

Getting there will require structural change, both within companies and in the larger health care ecosystem. As Jean-Paul Clozel of Switzerland-based Actelion Pharmaceuticals puts it, “if we are to sustain innovation at past levels, we will need to make changes that are both structural and cultural.” Internally, companies will need to develop and emphasize different core competencies. And in the larger ecosystem, different constituents will need to work collaboratively to realign rules, relationships and rewards.

New competencies

We interviewed four industry veterans to get their views on what competencies and processes companies will need to emphasize to address the imperatives discussed earlier (see spread on pages 14 and 15.) Based on

their insights and our own analysis, we have grouped the changes companies will need to make into four categories.

Market awareness. In an industry that has long been characterized by feast-or-famine swings in funding, biotech companies have traditionally been adept at tracking the sentiment of capital markets. In the new normal, that process will have to be applied more broadly, to closely follow changes not just in the capital markets, but also in the world of potential pharma partners, payers and regulators. As previously discussed, these constituents are facing tremendous pressures and are implementing radical changes in their own strategies, approaches and requirements.

That will require emerging company leaders with different backgrounds and skill sets. If the traditional emerging company leader had a strong science background coupled with relationships with the investor community, today’s leaders might additionally benefit from a deep knowledge of the requirements of payers and regulators, as well as relationships with pharma business development and strategy leaders.

As Christoph Westphal of Longwood Founders Fund puts it, “today more than ever, building value for investors requires a deep understanding of, and a healthy respect for, the business climate. Does the disease segment you’re focusing on already have many good treatments? Is this a well-differentiated mechanism? What will it take to commercialize this product? Do you have the resources to take it to market or to a key inflection point where you will attract handsome offers?”

Operating efficiently. We have already spent a lot of ink discussing the need to do more with less, and it is certainly not surprising that operating efficiency figured extensively in our interviews with industry veterans. Our discussion above highlighted *what* companies will need to do to boost operating efficiency, such as managing capital in different ways. But to pull this off will also require different skills, processes and incentives. Skills such as project management and discipline become more important, relatively speaking, than the attributes emerging companies have traditionally favored, such as the ability to tell a compelling scientific story to investors. Of course, project discipline does not just happen. It requires the support



of appropriate metrics and incentives – defining the financial and other metrics that matter, identifying the underlying drivers of those metrics, and measuring performance and tying incentives to those drivers.

As companies increase their utilization of virtual models, operating efficiently will also call for a different approach to managing relationships. As Mark Levin of Third Rock Ventures puts it, companies need processes for “handling outsourcing partnerships like strategic alliances rather than mere contractual arrangements. A successful virtual approach involves building genuine teams, soliciting input and spending time at partners’ sites.” CEOs need different skills, including, in the words of venBio’s Kurt von Emster, “strong project management, research and clinical oversight, and the ability to work across different time zones and personnel orientations.” And, of course, achieving all of this will require companies to develop appropriate incentives and align those incentives seamlessly across the extended enterprise.

Measuring and communicating value.

Given the prove-it-or-lose-it imperative, measuring and communicating value is a core skill set for biotech company leaders. While CEOs have always had to be good communicators, their focus in the past was to tell a compelling story to investors around the science. Today, attracting investors will take the ability to tell a broader story, including articulating plans to operate efficiently, and the ability to address changing payer and market dynamics. Historically, companies have often had an opportunistic approach to fund-raising – seizing opportunities when investor sentiment was positive. Going forward, it will be more important to have a strategic approach that includes developing a coordinated plan to address the imperatives discussed earlier, as well

as a coherent way of communicating that strategy. Once again, large company market access and reimbursement experience on the management team could be increasingly valuable in this new reality, and the widespread restructuring underway at big pharma – as well as personnel departures at large biotechs that have been acquired by pharma companies – could provide an attractive talent pool to draw from.

In addition, communicating value in the new normal will not just be about telling an appealing story. The story will need to be backed up by convincing data. Companies will therefore need to focus on acquiring analytical capabilities in fields such as statistics and pharmacoeconomics – through direct hires, alliances or contractual arrangements.

Karsten Henco of HS Lifesciences sums things up very well by pointing out that “a core competency of the CEO is the ability to understand how to build data packages that will be attractive to a pharma buyer – for instance, data based on clinical experience, which is very valuable these days. CEOs need to understand the structures of large companies and track changes that are taking place in their strategies and needs. This is far more difficult than selling a story to venture investors. And of course, quantitative skills in areas such as pharmacoeconomics are increasingly important.”

Business model innovation. Biotech companies have always responded to challenges with innovative approaches. Their remarkable resilience over the years has stemmed in no small measure from their ability to adapt quickly to shifts in investor sentiment, reinventing themselves when needed as genomics companies, platform players or drug-development firms to survive.



Going forward, that creativity and flexibility will be needed for developing new models and approaches to address the two imperatives described earlier. To some extent, the process has already started. In recent years, we have witnessed a surge of creative approaches for funding companies and conducting R&D – from project-funding approaches to fail-fast clinical trials to experimentation with more virtual models. (For a detailed discussion of these approaches, see “The new normal,” the *Introduction* article in last year’s *Beyond borders*.) Similarly, as biotech and pharma companies grapple with historic challenges, we have seen creative deal structures for bridging valuation gaps, sharing risk and assigning rights. We expect to witness even more of this innovation in the months and years ahead.

So far, most of the innovation has been driven by the need to do more with less. But as the imperative to prove it or lose it becomes increasingly important, we expect creativity to be applied to other areas as well. For instance, it will be critical to develop new models for engaging payers, who will become more important in the new ecosystem. (For one example, refer to *A closer look* by Silvia Ondategui Parra on page 18.)

A closer look

Payer marketing: a new business model for market access



Silvia Ondategui Parra

Partner

Ernst & Young S.L.

The historic business model of the biopharmaceutical industry is under increased pressure as public and private payers seek to reduce costs by demanding lower prices or by restricting market access for new products. Payers are increasingly willing to restrict or deny access to drugs purely on the grounds of price, especially if existing drugs already address the therapeutic area. Further, a dominant competitor can dictate reimbursement considerations for follow-on products. Even for orphan indications, in the absence of first-mover advantage, achieving premium pricing is becoming increasingly challenging.

Given the diminished opportunities in primary care, pursuing a specialty model has become more attractive. But even for specialty pharma products, the situation is changing, and a successful launch requires clinical trials that demonstrate clear clinical benefit in the target population; outcomes data that provide support for product value and that are linked to cost-effectiveness data; and a launch-price strategy that is sequenced carefully – particularly when multiple indications are being pursued.

To gain reimbursement at optimal prices in this challenging situation, a new model of “payer marketing” is emerging. Under this model, successful companies will approach pricing, reimbursement, health economics and outcomes from a more holistic market-access-driven perspective to effectively address each customer’s needs. A payer-marketing approach involves approaching payers as customers and segmenting them appropriately. Once segmented, appropriate messaging and relevant economic-outcomes support for each payer type can minimize potential access hurdles and ultimately drive commercial success.

As with most new models, a payer-marketing approach will require new core competencies in a range of job functions, from R&D to business development to marketing. An integrated price and market-access function can lay the groundwork for more effective teamwork and facilitate collaboration with payers, which will be critical to market-access success. Life sciences companies that are able to effectively build these competencies will have the best chance of optimizing product pricing and access.

We might see entirely new market offers being developed – either as a secondary focus and revenue source for existing companies or as the basis for entirely new start-ups. There will be tremendous opportunities for new business models built around data. After all, in the health ecosystem of the future, value will come from proof, and proof will require data. Biotech companies gather significant amounts of data during the long journey of product development, and all of that value has traditionally been monetized largely through the final product. It is worth examining whether the value of this information could be unleashed in other ways, e.g., to educate physicians or help patient adherence. There will be huge opportunities in devices and diagnostics as well. Diagnostics that can help target medications to differentiate them from competitors will become increasingly important.

In addition to developing new offers, biotech companies could apply some of these new technologies and data sources to making drug development more efficient and relevant. Much of pharma's innovation around the prove-it-or-lose-it imperative has been focused on the commercial end of the value chain. While most biotech companies are years away from commercializing products, we still think there are tremendous opportunities for R&D-focused companies to develop new approaches and models. For instance, pharma companies have been partnering with social media sites to better understand how physicians and patients are using their products. But those same sites could also be used for other purposes. Collaborating with online communities that bring together patients with a specific disease could make clinical trial enrollment faster and more efficient. Similarly, a social media site for patients could provide useful insights into

aspects such as drug delivery – a company developing an inhalable insulin, for example, might want to know whether patients would rather have a delivery mechanism that is pain-free or less bulky. Dennis Purcell of Aisling Capital identifies the potential latent in such approaches, pointing out that “companies need to involve patients and patient advocacy groups earlier. Not only can these groups help speed clinical trial enrollment and FDA interactions, but they also allow companies to gain early assessments of the ultimate commercial prospects for new therapies.”

To sum up, successfully addressing the two key imperatives of the new normal will require a very different approach that builds and emphasizes new sets of core competencies. Biotech has long been “the business of science” – an industry that has tried to build commercial undertakings based on a passionate belief in the science. Today, companies instead need to focus to a greater degree on “the science of business” – bringing disciplined, market-aware, business-savvy approaches and processes to the unprecedented challenges they face.

Coordinated action

Addressing the two key imperatives of the new normal will take more than changes to companies' processes and competencies. It will also require changes beyond corporate walls. Biotech companies exist in a complex health care ecosystem that includes patients, providers, pharmaceutical companies, medtech companies, private and government payers, regulators, policy makers, employers, universities and many others. Many of the changes necessary to truly move to a health outcomes-based system cannot be undertaken by biotech companies alone. They will require changes to the structures, incentives

and value flows between different actors, which can only be achieved through coordinated action.

It is not surprising that the need for coordinated action affects both ends of the biotech business: funding – where coordinated action with investors and policy makers could change incentives – and innovation – where coordinated action with regulators and payers could improve the daunting odds of bringing products to market. Lastly, in an era of sweeping change, companies will need to work with all key constituents to build trust and help shape the debate, as discussed below.

Regulatory approvals. As discussed earlier in this article, one of the biggest sources of strain on the innovation end of the biotech business model is that regulators have become exceedingly cautious about approving products in recent years. For companies and investors, this makes the economics more challenging by raising the level of risk and lowering returns on investment. “The [FDA] has effectively discouraged investment – whether by large companies or VCs – in whole fields, from obesity to diabetes to cardiovascular disease,” says David Gollaher of the California Healthcare Institute.

Meanwhile, Karen Bernstein of BioCentury points to a potential solution: “Everyone would be better off,” she argues, “if we ditched the rigid Phase I-II-III-approval model and went to more adaptive trials and conditional approvals with large patient registries to collect robust safety and efficacy data.”

While adaptive clinical trials have been discussed by industry insiders for a while, they have gained little traction. Yet proponents argue that R&D would become much more productive and efficient if the

rigidity of the current drug approval system were reduced. This system, based on the scientific method, involves establishing a hypothesis at the outset, and then proving or disproving it in a series of clinical trials. But the initial hypothesis and trial design involves considerable guesswork (e.g., in selecting the dosage), based on scant information. And since trials are double-blinded, there is little opportunity to make adjustments based on information gained along the way. Adaptive trials, on the other hand, can allow for real-time adjustments based on real-world information – enabling more efficient use of resources and permitting product candidates that might otherwise have failed to come to market as more efficacious treatments.

Conditional approvals would inject further flexibility into the approval system by allowing regulators to approve products earlier (e.g., after a successful Phase II trial) while requiring the ongoing collection of

additional real-world data to measure safety. While this pathway would not be open to all drugs, it could be used selectively in areas of unmet need (e.g., where no drug currently exists).

The premise underlying these solutions – that in a world where data sources are vastly more abundant and computing capacity is vastly more powerful, we can make better decisions if we unleash the potential of real-time information – has proponents well beyond the drug industry. For instance, a venture called the Billion Prices Project scours large numbers of e-commerce sites for price changes to produce inflation data that is far more timely and relevant than the official numbers published by government economists (whose long-standing methodology involves conducting a monthly survey, then analyzing the data and publishing it – meaning that the numbers are several weeks old by the time they are released).

Payment mechanisms. Biotech companies will also need to work with payers to realign payment mechanisms around health outcomes and value. In the US, for instance, Medicare is essentially a cost-plus, activity-based system that pays providers a flat rate for each intervention or procedure. To be truly aligned around outcomes, payers will instead need to measure the value each intervention adds to the health care system and pay accordingly. The industry will need to work with payers to frame the discussion more holistically – focusing not just on the price tag of drugs, for instance, but on the overall cost and benefit relative to other interventions.

One could point to any number of other distortions in current payment mechanisms, from reimbursement levels for companion diagnostics to the perverse behaviors produced by reference pricing. Yet removing these distortions is no trivial matter since every change produces winners and losers.





The latter group can often vociferously resist reforms, which is precisely why coordinated action becomes essential.

Investor incentives. To alleviate the increasing strain on biotech funding, companies will need to work with policy makers and other stakeholders to develop solutions to boost investor returns to levels more commensurate with the risk they are currently taking. For instance, companies and investors are often shying away from developing therapies for chronic and degenerative diseases because of the growing risk and cost in these segments, even though the world will desperately need such drugs in the years ahead, thanks to aging populations and rising standards of living. At some point, it may be necessary to introduce economic incentives for these indications, much as policy makers did a generation ago for rare diseases.

At a time when exits are challenging and returns are squeezed, it would be helpful to consider incentives for private capital to carry the baton farther. For example, policy makers could allow deductions of R&D expenses to pass through immediately to investors, much like structures used previously in the oil and gas industry, thus helping investors mitigate the downward pressure on returns. In addition, reducing or eliminating capital gains taxes in specific therapeutic areas could encourage investment in certain indications.

Building trust. Underlying the three areas just discussed is a broader need for coordinated action to build trust. Indeed, any efforts to jointly develop solutions will only be successful if there is a foundation of trust among the industry, policy makers, payers and regulators. That trust has diminished somewhat in recent years as the public perception of drug companies has plummeted (primarily with respect to

big pharma, though biotech has not been entirely unscathed). So it is not surprising that, while drugs constitute only a small percentage of overall health care costs, drug companies are often excoriated in the policy debate – and price controls are often held up as the best solution for restraining health care costs.

The need for trust will become all the more important as drug companies – like all the players in the health care system – face a future with far more scrutiny. In this regard, Henri Termeer's comments about orphan drugs in *Beyond borders 2008* may again prove prescient: "At the end of the day we need to demonstrate that our products deliver value, we need to be transparent about pricing, and we have to address questions about access and affordability." Once again, as in orphan drugs today, so in the entire industry tomorrow. As they work more closely with payers, it will become increasingly critical for companies to be transparent about the cost and value of their products. And the new models they develop will need to address issues of access and affordability to build trust with payers and, equally important, with patients.

Outlook

The measures described above – doing more with less, proving outcomes and value, developing new competencies and working jointly with other stakeholders – are a good list of steps that companies can take to sustain innovation. But will they be enough? Will we be able to restore innovation to historical levels? It's hard to say since it largely depends on the success of the industry at implementing the changes.

The mitigating factor is that biotech companies are not in it alone. Indeed, the same basic pressures – the need for greater efficiency and the drive to align behaviors

with outcomes – are becoming more acute for everybody in the health ecosystem. And therein may lie biotech's salvation.

For instance, pressure from policy makers and regulators will start to ease as they confront an increasingly untenable situation because of the inexorable march of demographic change. Aging populations in many major markets – the US, Japan, Europe, China – will ultimately intensify the pressure for new treatments for degenerative and chronic diseases. Meanwhile, in emerging markets, growing middle classes will create similar pressures as the burden of chronic disease becomes more acute. Today's regulatory caution was not created in a vacuum. Rather, it has been driven by pressure from policy makers – who will adjust when they are faced with a more dire challenge from health care costs and more urgent demands from voters for effective treatments. It will then become necessary to recognize that substituting drugs for inpatient care is one of the most effective ways to bend the cost curve.

Until that day arrives, it is important not to forget that the same basic pressures are also affecting biotech's more traditional partners – from venture capitalists to pharma companies. With everybody facing the same imperatives, the other members of the health ecosystem will need to collectively develop creative solutions in the years ahead. We've already seen a rise in innovative approaches and models since the onset of the crisis. Brace yourselves, because there's more creativity ahead. ►

A reordering is in the works



George A. Scangos, PhD
Biogen Idec
CEO

We all know the challenges that are facing our industry. Historically, they have included complex global matters such as R&D productivity, pricing pressures, regulatory barriers, financing issues and a daunting legal climate. More recently, we can add to that list an increased emphasis on drug safety, a global financial crisis, and the beginning of US health care reform, which by itself will unlock a wave of industry challenges from comparative effectiveness to the Independent Payment Advisory Board (IPAB) to a new biosimilars framework.

Adding to these challenges is the ever-mounting pressure from shareholders seeking near-term gains in a sector based on long-term, high-risk bets. They are driving a reformist agenda that includes a greater voice in the boardroom, stronger corporate governance and downward pressure on spending.

What is a rational biotech executive to make of all of this?

Aligned interests

It is important to acknowledge that the demands of our major stakeholders are important, rational and even healthy for our industry. Shareholders have a right to expect a return on their investment – that is why they invest. Patients have a right to expect us to do right by them – indeed, they count on us to do so. Health care providers have a right to expect us to provide them with timely, accurate and reliable information. Employees have a right to be treated fairly and work in an environment that is stimulating, challenging and enriching.

Yet, members of each of our stakeholder groups are unhappy with the way the industry operates. They believe that we don't innovate enough – or quickly enough. They believe that we spend too much money on unproductive activities, including sales and marketing and R&D. They mistakenly believe that we care more about profits than about patients. Given the way our industry sometimes behaves, it is not hard to understand where these concerns come from, and they are not completely without merit.

However, having worked in the industry for 25 years, I know that the vast majority of people working in biotech are committed and caring and have chosen this industry because of the potential to *improve patients' lives*. And therein lies the realization that the interests of our stakeholders are better aligned than it may sometimes appear.

For drug companies, success stems from putting patients first. We exist to bring better therapies to patients. If we fail to do that, we have no business being in business. The "patient first" philosophy is not simply altruistic – it is good business. We live in a zero-sum world of fixed budgets and financial constraints. Maximizing the good we do for patients means using our resources in the most productive and efficient way. Money spent on projects that are ill-conceived, poorly executed or years behind the competition will not benefit patients and will prevent spending on other opportunities that could provide a true benefit. So, what is in the best interest of patients is usually in the interest of shareholders as well.

At Biogen Idec, for instance, we are determined to build long-term value without sacrificing the near-term financial objectives of the company. Shortly after I started with the company, we took several steps to better align our interests with both patients and shareholders. Strategically, we focused on our strengths – e.g., expertise in neurology, immunology and hemophilia as well as biologics R&D and manufacturing – while terminating our efforts in cardiovascular medicine and oncology. We instituted a "no dabbling" rule: we will be among the best in the world at what we do, we will work with others who are among the best, or we will get out of that business. At the same time, we made the difficult but necessary decision to consolidate our sites, including shutting down our San Diego operations, and we reduced our headcount by approximately 13%. We instituted a strong program management system to improve the crispness and timeliness of decision-making and execution.

These measures are obviously good for shareholders – we expect to realize annual savings of approximately US\$300 million. But they are good for patients as well – we are a stronger company with more resources to fund initiatives that truly are value-added, maximizing the potential for bringing meaningful new therapies to patients. And these initiatives are also in the best interests of our employees – the changes have been difficult for employees who lost their jobs, but the company is a better place for the employees who are still here.

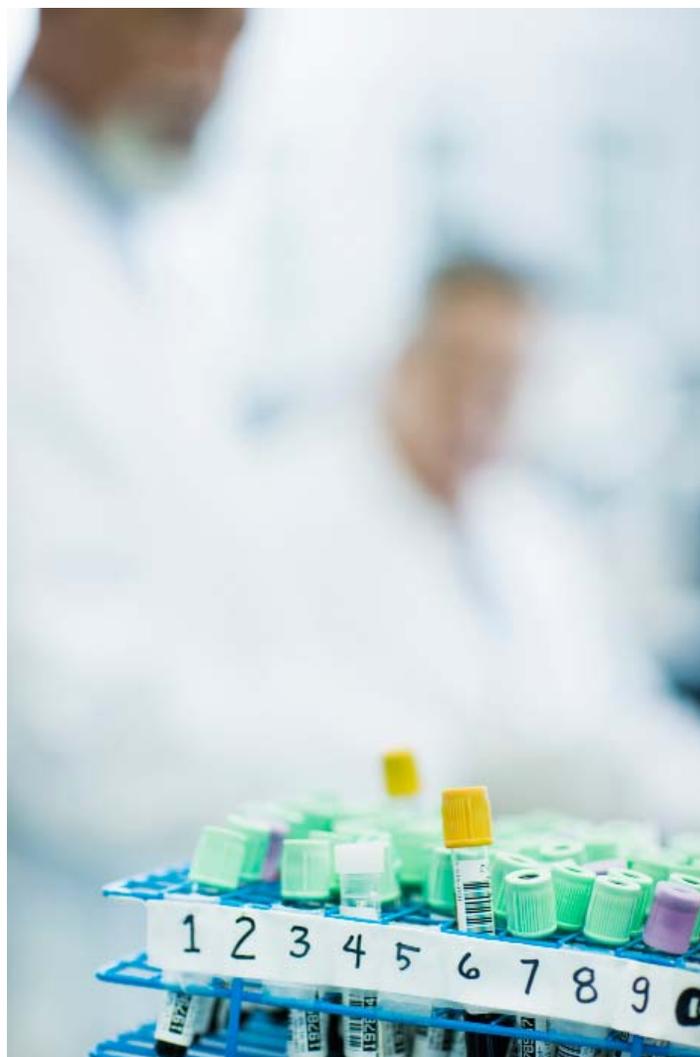
Challenges

The fact is that R&D does cost too much and take too long. Smaller biotech companies, which exist because of their potential and their dreams, are subject to the same set of issues as larger companies but have to face them with fewer resources, less breadth of expertise and fewer degrees of freedom. These pressures result in more product-focused companies and fewer technology platform companies, more companies whose strategy is an M&A exit and fewer companies being built for the long term.

These trends present an opportunity for larger companies, since there are many more small companies willing to be acquired. But they also present a challenge, which is a relative dearth of new technologies and platforms. This void is being filled by universities, many of which have turned to drug discovery and translational medicine as a funding source. The structure of the entire biomedical R&D effort in the US is being redefined. Each of the segments of the enterprise is seeking new ways to work with the others. Whether these changes are good or bad, they are real and they are here. Understanding how to operate in the changing industry structure will be a key competitive advantage as we move forward. To this end, I often hear people talking about combining “the best of pharma with the best of biotech” or “the best of biotech with the best of academia.” These are noble concepts that are easy to understand but difficult to operationalize, and I have seen few successful examples. But given the difficult environment that we all face, it is imperative that we figure this out. I think there are some general guiding principles that will help:

1. We all tend to trivialize what we don't understand. Many academics trivialize drug discovery and development, and many larger companies undervalue true innovation and risk-taking. We will need to fairly acknowledge the expertise that each party brings to the table.
2. Trivializing what we don't understand leads to undervaluing the contributions of potential partners. If we are going to work together over the long term, we need to be flexible and fair in how we share risk and rewards.
3. We need to look hard in the mirror. We have to acknowledge our weaknesses and deal with them. It isn't necessary, and maybe not even possible, for a company to be good at everything. What is important is to identify areas of weakness and strengthen them, eliminate them, or work with others who excel in those areas.

We are entering a period that poses amazing opportunities as well as serious threats to our industry. It is imperative that we seize the opportunities and face up to and deal with the threats. The opportunities are truly awe-inspiring and have the potential to lead to substantially improved therapies for most diseases, shorter and less expensive development paths and potentially lower health care costs. I believe that the way to seize the opportunities and face the threats is to be realistic about our capabilities, focus on excellence in all that we do, establish fair and mutually beneficial collaborations and be very careful about how we spend our resources. If we can do all that, we have a good chance of delivering better therapies to patients and better returns to our investors. ►



Boosting innovation: a scientific method



Mark Fishman, MD
*Novartis Institutes for BioMedical Research
President*

More than ever, the life sciences industry needs to revitalize its approach to drug discovery. Patients are waiting. Large pharmaceutical companies, facing significant revenue declines due to blockbuster patent expirations, need innovative new products to fill the gap. For smaller firms, a challenging capital environment is constraining the ability to fund R&D. Meanwhile, pressures from regulators and payers are making it more difficult for companies to bring innovative products to market. While the current financial and regulatory climate is gloomy, the climate for innovative science and medicine has never been brighter.

At Novartis Institutes for BioMedical Research (NIBR), Novartis' global research organization, drug discovery is flourishing. Since its creation in 2002, NIBR has developed one of the most productive pipelines in the industry, with 143 projects in clinical development – 63 of which are new molecular entities. We do not claim that we have invented a panacea. Rather, we harness a constellation of approaches that when integrated together, contribute to success.

1. Choose the right projects. We do not select research programs based on potential market size, but rather based on unmet medical needs and scientific tractability. In other words, we focus on the patient and follow the science. This approach has three implications.

First, it has led us to **focus on rare diseases**. What makes these diseases attractive is that they are mechanistically well understood – making tackling the scientific challenges simpler and the development more efficient. The mechanisms that underlie these diseases are usually shared by more common diseases, so understanding them can shed light on multiple ailments. So our approach is often to start by developing a drug for a rare disease and then apply it to more common ones later.

Second, we **ignore financial models and pharmacoeconomics** – at least in the early phases, where NIBR is focused. Economic analyses conducted before human proof of concept (Phase IIa) are of little value, since they are heavy on assumptions and light on real information. If you're not careful, you can get enamored of elegant – but ultimately misleading – models. This may go against the conventional wisdom, which says you should conduct pharmacoeconomic studies much earlier

in the development process, but I firmly believe that if you can address true unmet medical needs, the economics will take care of themselves.

Third, we **embed physicians** into the process early on. This is essential if you intend to focus on patients and unmet medical needs. Physicians bring valuable and unique insights that help us choose our targets and design proof-of-concept clinical trials.

2. Follow molecular pathways. We have organized our drug discovery efforts based on molecular pathways. While the human genome has about 22,000 genes, there are only a few dozen molecular pathways. The advantage of targeting pathways is that we can find the key nodes within them that we can target with drugs. Ultimately, we hope to divide diseases by the pathways that go wrong instead of by the organ systems they affect. In principle, one drug could be effective in treating several different diseases.

3. Attract the best talent and create a supportive culture.

We strive to make sure our scientists are in the right roles.

Then we give them the authority and freedom to do their work, removing bureaucracy and supporting them through an open, transparent and science-driven culture. Our discovery scientists are **encouraged to publish**, while our postdoctoral fellowship program provides opportunities to collaborate with scientists from academia on multidisciplinary research projects.

4. Use the right metrics. When implementing any strategy, it's important to measure progress. But it's also important to make sure you are measuring the right thing, since you get what you measure. Our work is subject to a high degree of review.

We have a scientific advisory board with outstanding scientists who get very deeply involved in the details of the science and bring an outsider's perspective. In addition, our board of directors has its own group of scientific experts to review our progress. In both cases, we try to make sure that we are measuring what matters – whether the science and medicine are going in the right direction – rather than imposing some artificial metrics that monitor particular phases of the pipeline.

At a time when we desperately need more productive and efficient drug research, the principles we are following at NIBR may have broad applicability. There is no single magic bullet. Get back to the science. Focus on unmet medical needs rather than beautiful economic models. If you make a medicine that meets a need and has a high impact, it will get reimbursed. I cannot predict prior to proof of concept – nor can any pharmacoeconomic model – what the reimbursement will be, but you will make money and, more importantly, you will help patients. ►

Reaching for growth

Country profiles



Snapshots from Asia



China: funding innovation



Norman Chen
Fidelity Growth Partners Asia
Partner

China's health care investment environment is developing rapidly. The Chinese government has undertaken massive health care reforms, earmarking more than US\$125 billion to upgrade infrastructure and stimulate domestic life sciences research. These stimulus programs, combined with a rapidly increasing Chinese middle class, have grown the health care market by more than 20%-25% per year. This dynamic market is in turn attracting a wave of new domestic and Western venture capital and private equity investors, creating an increasingly competitive health care investment market in the country.

While the Chinese industry is still at an early stage of development, we see opportunities across all subsectors – pharma, devices and services – and expect to continue investing in all of them. More remarkably, we are increasingly investing in *innovative* Chinese companies. In the pharma segment, we previously funded specialty pharmaceutical companies where there was little technology risk and the focus was on sales, marketing and distribution. But with China-based R&D companies showing promise of success over the next three to five years, we are now starting to invest selectively in innovative drug development firms.

Similarly, in the medical devices space, the play in the past was import-substitution companies that made reasonable-quality devices – such as stents, patient monitors or orthopedic devices – to replace products of multinational competitors. We believe that trend is largely complete and we are increasingly looking at innovative medical device companies with Chinese and/or global intellectual property. Lastly, we are also investing in innovation-based medical services companies that offer superior clinical care and a higher-quality “patient experience.” Although this type of innovation is more “know-how” than intellectual property, it still provides meaningful competitive advantage.

India: rapid growth



Utkarsh Palnitkar
Pluripotent Capital
Managing Director

India's biotechnology sector – the third-largest in the Asia-Pacific region, after Australia and China – continues to grow at a rapid clip, tripling in size in the last five years alone. With the exception of a few large diversified companies, the bulk of the industry consists of small and medium enterprises, many of which are engaged in contract services and vaccines, areas where India continues to have a significant competitive advantage. More recently, many Indian companies are recognizing tremendous potential in biosimilars, and a number of pharmaceutical companies have sprouted biotech branches primarily to exploit this opportunity.

Despite the sector's rapid growth, relatively little funding is available for innovative biotech R&D. Of the US\$3 billion invested in Indian health care and life sciences over the last decade, only US\$90 million has gone toward innovative biotechnology. Even here, investments have predominantly focused on manufacturing and commercialization. Investors have shied away from discovery-stage enterprises, which are still relatively nascent, though a growing number of companies are emerging.

The Government of India has attempted to bridge the gap in early-stage funding through a number of innovative programs, such as the Small Business Innovation Research Initiative. This program provides grants and loans to biotech start-ups in pre-proof-of-concept and early stages of development. Meanwhile, the Biotechnology Industry Partnership Program supports “breakthrough research.” In addition to these funding initiatives, biotech funding could receive a major boost with the emergence of life sciences dedicated funds such as Pluripotent Capital, as opposed to sector-agnostic funds that make some investments in life sciences.

🇯🇵 Japan: cautious optimism



Yoshihiro Ohtaki
Biofrontier Partners
General Partner

Over the last 15 years, Japan's government and universities have worked with the private sector to develop the infrastructure needed for fostering innovative start-ups. As a result of these efforts, approximately 500 venture-backed biotechnology companies were established in a short period of time. While these firms grew steadily for many years, the emerging biotechnology sector was hit hard by the combined impact of two major economic upheavals. The first of these crises, the 2006 Livedoor financial scandal, brought down a high-flying internet company and cast a pall over the market for start-ups. This was exacerbated by what is referred to in Japan as the "Lehman Shock": the September 2008 bankruptcy of US-based Lehman Brothers, which precipitated an international financial contagion that shook up Japanese markets. The stock market for emerging Japanese companies all but collapsed. It has consequently become extremely difficult for emerging Japanese companies to secure the funding needed for growth.

Still, there are grounds for hope. An increasing number of venture-backed biotech companies have achieved a certain degree of growth and are ready to go public. Rapidly growing stock markets in other Asian countries could provide a receptive location for such listings. Indeed, we have seen more and more of these growing companies aiming for such listings in the recent past. Meanwhile, government policy continues to actively promote the life sciences, and investor sentiment toward biotech has also been gradually recovering.

Needless to say, the recent Great East Japan Earthquake will have a major impact on the Japanese economy. Now is the time for Japan to reflect upon itself and show its true strength by rebuilding the country, working together with the younger generation. I remain cautiously optimistic.

🇦🇺 Australia: good news, bad news



Geoff Brooke
GBS Ventures
Managing Partner

Australia's biotech investment market is a tale of good news and bad. The good news is that investors have several recent examples of Australian companies that have successfully been acquired by, or signed partnerships with, larger corporations – sometimes for staggering amounts. Since March, cash offers have been made for ChemGenex by Cephalon (US\$240 million) and for Celestis by Qiagen (US\$360 million). This comes on the back of a number of significant technology-validating partnerships secured by Australian biotechs, such as Acrux's deal with Lilly, which has driven the Acrux market cap to close to US\$1 billion. Similarly, Mesoblast signed a license-and-equity deal with Cephalon that has sent its market cap skyrocketing to more than US\$2.5 billion. Waiting in the wings are other public companies that could make attractive targets – including Sunshine Heart, Bionomics, Alchemia, CogState and QrXPharma – as well as private biotechs with products in late-stage clinical trials positioning themselves for global exposure.

The bad news is that, even as these success stories are proving the viability of biotech investing, capital for younger companies is close to nonexistent. The federal government has eliminated a highly useful grant scheme for technology companies and appears ready to decimate its allocation of funds to medical research grants – the lifeblood of new company development. Furthermore, the global financial crisis has driven the largest pool of Australian capital, retirement (superannuation) funds, away from private equity (and, indeed, away from all but a very small number of venture funds).

How will we fund the creation of future success stories? Despite a raft of good news, a cloud of uncertainty hangs over the future of Australian biotech.

Reaching for growth

China: laying the foundation for innovation

A rising superpower and the world's most populous country, China is on the path to becoming a significant biotech player. Although the domestic drug industry has a large number of small players, the Chinese life sciences industry had a strong year in 2010, with VC investments, IPOs, M&A deals and government funding all reaching new highs.

Investors: seeking opportunity

According to ChinaBio, life sciences venture capital and private equity investments exceeded US\$1 billion in 2010, an increase from the US\$300 million-US\$400 million seen in recent years, with 63% of that total directed at biopharmaceutical enterprises and the remainder split between service and medical device companies. While health care is clearly a sector favored by VC and private equity firms, much of the capital has gone to commercial-stage companies. However, as Norman Chen of Fidelity Growth Partners Asia notes (see page 26), the number of R&D-focused companies is increasing and VCs are beginning to invest selectively.

China has become the IPO leader globally as investors seek to capitalize on the sector's significant growth opportunities. Life sciences IPOs in China continued to increase in 2010, both in number and volume. According to ChinaBio, the 33 IPOs in the life sciences industry raised an aggregate US\$5.9 billion in 2010, an increase of 47% over 2009. While these numbers are impressive, most of the IPO funding (as with private capital) has gone to mature, profitable companies, making comparisons with the US and Europe of limited relevance. What remains unclear is whether investors in China will have the risk tolerance and the patience to back the development of

innovative technologies as companies emerge from the various government-supported initiatives discussed below.

In addition to making R&D investments, global companies are actively seeking alliances or acquisitions to leverage the domain knowledge of local players and to expand their local presence. For example, GSK acquired Nanjing MeiRui for US\$70 million in January 2011 to expand its China presence through Nanjing MeiRui's portfolio of urology and allergy products as well as its sales platform and manufacturing facility in Nanjing. In February 2011, Sanofi completed its acquisition of Chinese consumer health care company BMP Sunstone for US\$520.6 million to expand its Chinese

business through BMP's portfolio of products and its distribution network. And in April 2011, Pfizer and Shanghai Pharmaceutical signed a memorandum of understanding to develop and commercialize a Pfizer product in China. The two companies will also explore other possible partnerships and are already partnering to promote Pfizer's Prevenar vaccine in China. Full acquisitions of drug companies by multinationals are still relatively uncommon, as acquirers must assess and manage the operating risks associated with many target companies, particularly in the area of payments to health care providers. The most significant acquisitions completed in 2010 were focused on distribution companies, while the biggest M&A story of the year

Select Chinese biopharmaceutical IPOs, 2010

Company	Month	Exchange	Amount raised (US\$m)
Inner Mongolia Free Han & Mongolia Pharmaceutical	January	Shenzhen ChiNext	81.0
Guizhou Xinbang Pharmaceutical	April	Shenzhen Mainboard	104.9
Tianjin Lisheng Pharmaceutical	April	Shenzhen Mainboard	303.3
Shenzhen Hepalink Pharmaceutical	April	Shenzhen Mainboard	869.3
Lansen Pharmaceutical Holdings	May	Hong Kong	78.7
Hainan Honz Pharmaceutical	May	Shenzhen ChiNext	219.7
Guizhou Bailong Group Pharmaceutical	May	Shenzhen Mainboard	216.8
Guangdong Pibao Pharmaceutical	June	Shenzhen Mainboard	109.1
Harbin Gloria Pharmaceuticals	June	Shenzhen Mainboard	256.2
Chongqing Zhifei Biological Products	September	Shenzhen ChiNext	223.5
Walvax Biotechnology	October	Shenzhen ChiNext	355.5
Guangdong By-health Biotechnology	December	Shenzhen ChiNext	225.8
Xiangxue Pharmaceutical	December	Shenzhen ChiNext	158.1

Source: Ernst & Young, BioCentury and Cowen Latitude

turned out to be a deal that wasn't: Charles River Labs' proposal to acquire Wuxi PharmaTech for US\$1.6 billion was withdrawn after Charles River shareholders objected to the transaction.

Government: reform, investment and growth

As discussed in the 2010 edition of *Beyond borders*, the Chinese government is in the midst of fundamental reform of the health care delivery and payment systems, which will directly impact how drugs are manufactured, distributed and reimbursed. Reforms have also been undertaken to strengthen the intellectual property regime and drug approval process.

On the innovation front, in 2010, the guidelines for China's 12th Five-Year Plan (FYP) (2011-15) for national economic and social development were unveiled. The latest FYP continues to identify biopharmaceuticals as one of seven strategic emerging industries. The Government expects to invest RMB40 billion to support the industry over the five-year period, RMB10 billion of which will come from the central government.

In November 2010, the Ministry of Industry and Information Technology, Ministry of Health, and State Food and Drug Administration (SFDA) issued the Guidelines for Accelerating Restructure of the Pharmaceutical Industry as part of the country's health care reform goals. Among other objectives, the policy guidelines aim to strengthen the discovery and development of new products and technologies, champion the establishment of large pharmaceutical



groups through consolidation and enhance global competitiveness in the next five years. The guidelines include targets for industry consolidation (at least 80% of the drug market controlled by the top 20 manufacturers) and for new drug introductions (at least 10 new small molecule and 15 biologic drugs originating from China).

Following the controversy surrounding the marketing of substandard rabies vaccines in 2010, the SFDA and the Ministry of Health jointly launched a supervision and examination program to effectively enforce and strengthen quality assurance in vaccine production, circulation and inoculation. Early in 2011, the SFDA also announced amendments to Good Manufacturing Practice (GMP) regulations. The new GMP regulations apply the concepts of quality risk management and

process control of drug manufacturing. Newly established facilities will be required to immediately comply with the new standards, while existing production facilities for blood products, vaccines, injections and other sterile pharmaceutical products will be granted a transition period until December 2013. Manufacturers of other pharmaceutical products will have until December 2015 to comply with the new requirements.

India: exploring new opportunities

India is well poised to explore innovative areas such as molecular diagnostics and personalized medicine, and to capitalize on its existing strength in biosimilars. And amid a growing global focus on renewable energy, the country appears to be ramping up its efforts in industrial biotechnology.

Innovation opportunities: molecular diagnostics and personalized medicine

While many Western companies have made significant inroads into personalized medicine, the field is relatively nascent in India. However, companies and the government are increasingly focused on opportunities in this area. India's first-ever sequencing of a human genome was completed in 2009 by scientists at the Institute of Genomics and Integrative Biology (IGIB) in Delhi. In 2010, the Indian Council of Medical Research, India's leading biomedical research body, set up a task force to focus on specific research topics within pharmacogenomics. Companies such as Tulip, Span Diagnostics, Beacon Diagnostics and TransAsia Bio-Medicals have established their presence in niche diagnostic areas. Many Indian companies have also started offering pharmacogenomic tests, primarily in cancer and cardiovascular disease, including Avasthagen, OncQuest Laboratories, Acton Biotech, TCG Life Sciences, Advinus Therapeutics and Jubilant Biosys.

Deal opportunities: biosimilars to the forefront

With over 40 deals completed in 2010, strategic alliances continue to gain momentum. With low-cost manufacturing

capabilities and strengths in small-molecule generics, Indian companies are well positioned to benefit from the estimated 48 biologics – with sales of US\$73 billion – that are slated to go off patent in the next decade. Building on a surge of biosimilar product launches in 2009, the segment saw a spate of strategic alliances and asset acquisitions in 2010.

The year's noteworthy deals included Ranbaxy Laboratories' acquisition of Biovel Lifesciences, Biocon's commercialization agreement with Pfizer (the company also announced plans to establish R&D centers in Malaysia) and Cipla's acquisition of a large stake in MabPharm and BioMab.

Government: supporting growth

With limited access to venture capital and few companies pursuing an IPO, the government has played a key role in

supporting the industry. The industry has had a high level of funds allocated in the Government's Eleventh Five Year Plan (2007-12), and the industry is waiting to see whether this level of support will continue in the next Five Year Plan.

To expand access to health care among the rural poor, India's Ministry of Labour and Employment launched the Rashtriya Swasthya Bima Yojana (RSBY) program in 2008. This state health insurance program – which appears on track to become one of the world's largest – has already quadrupled India's health insurance penetration by covering 23.5 million households in its first three years. This growth has created an attractive market for entrepreneurs interested in developing hospitals and clinics that can serve India's rural poor as well as opportunities for India's life sciences industry as a whole.

Select Indian deals, 2010

Company	Acquired or partner company	Type	Month
Ranbaxy Laboratories	Biovel Lifesciences	Acquisition	January
Ranbaxy Laboratories	Pfenex	Development agreement	March
Cipla	MabPharm and BioMab	Stake acquisition	June
Piramal Healthcare	Bio Syntech	Acquisition	June
AstraZeneca	Intas Pharma	Supply agreement	September
DM Corp.	Orf Genetics	Development agreement	September
Greater Pacific Capital LLP	Accutest Research Laboratories	Majority stake acquisition	September
Pfizer	Biocon	Commercialization agreement	October
Rallis India	Metahelix Life Sciences	Majority stake acquisition	December
Strides Arcolab Limited	Inbiopro Solutions	Stake acquisition	December

Source: Ernst & Young, media reports

Other notable government initiatives include:

- ▶ In 2010, the central government announced plans to set up a Rs 100 billion (US\$2.2 billion) venture fund for supporting drug discovery and research infrastructure development projects.
- ▶ In collaboration with private players, the central government and various state governments continue to fund infrastructure investment, especially through biotechnology parks.

Regulatory reforms: toward standardization

In an effort to create efficiencies and streamline the drug approval process, the Department of Biotechnology introduced the concept of a single, autonomous regulatory agency – the National Biotechnology Regulatory Authority of

India (NBRA) – to oversee the process. It has been almost three years since the initial proposal in July 2008, but the industry hopes that the NBRA bill will be taken up in the current 2011 session of Parliament.

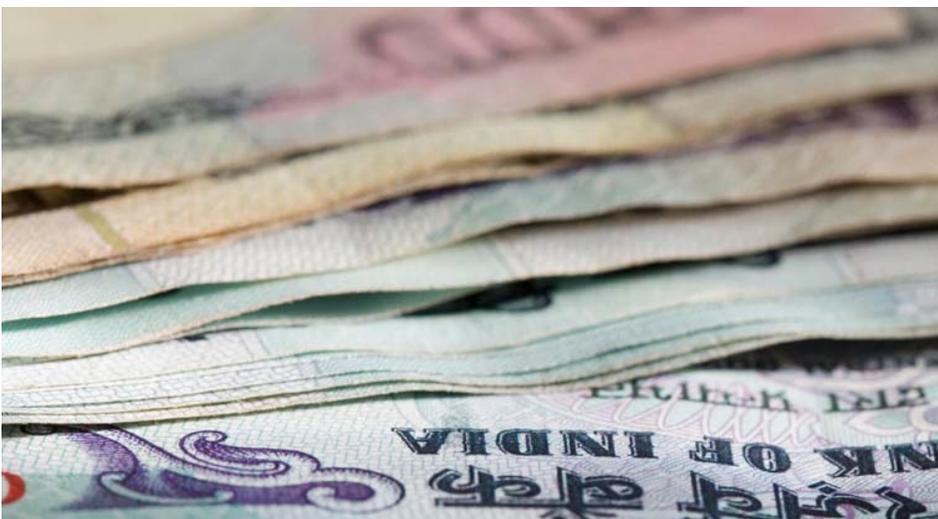
In a move to standardize procedures, Parliament passed the Clinical Establishments (Registration and Regulation) Bill in 2010. This bill seeks to make the registration of all clinical establishments mandatory in the country. The law will come into force across the country once the states adopt it in their Assemblies.

The Central Drugs Standard Control Organization amended its guidance for post-marketing changes in biological products. By removing provisions for automatic approval of post-marketing changes, the agency is requiring that companies apply for new drug or manufacturing licenses.

The industry is pressing the government for speedy approval of the proposed biosimilar guidelines to align standards with those of international regulatory systems.

Outlook: opportunities ahead

With increased financial assistance and opportunities, the biotechnology industry continues to make progress. Multinational companies have been able to penetrate India's market – and tap into its intellectual wealth – by setting up equity and technology collaborations with Indian firms. The biosimilar sector will continue to draw attention, leveraging India's strengths in small-molecule generics. The biofuels segment also looks promising for large-scale expansion, with partnerships with US companies now in place to develop second-generation biofuels such as algal biodiesel and cellulosic ethanol.



Brazil: fueling growth with investments and reform

Brazil has a leading position in agricultural biotech and biofuels, enabled by its strong natural resource base and industrial policies focused on encouraging innovation. However, future growth will be shaped by its evolving intellectual property regime, where much remains to be achieved, despite recent improvements.

Investments in biofuels

Global oil majors are becoming increasingly interested in the green-energy potential that Brazil – the world's largest sugarcane-based ethanol market – has to offer. In 2010, the country continued to attract investments from domestic and foreign players. Of the US\$5.6 billion invested in biofuel production in 2010, Brazil drew the biggest share, approximately US\$1.8 billion, followed by the US and Europe.

Agricultural biotech: accelerating approvals

Brazil – already the world's second-largest biotech crop-cultivating country with 17% of the world's biotech acreage – had the world's largest year-on-year increase in absolute biotech crop planting, according to the International Service for the Acquisition of Agri-biotech Applications' 2010 annual report. Strong support from the recently elected president of the National Biosafety Technical Commission (CTNBio) – the agency that grants approvals to biotech crops – has accelerated approvals.

Biopharmaceutical players: on the expansion track

Several multinational biopharmaceutical companies have begun to focus on Brazil in their strategic growth plans. In early 2011, Amgen expanded its Brazilian operations with the acquisition of Bergamo, a privately held pharmaceutical company, for US\$215 million. Amgen also reacquired the rights to some of its innovative products that were previously sold to domestic player Hypermarcas. Sanofi entered an innovative collaboration with Fundação Biominas in March 2010 to advance R&D in Brazil, with a particular focus on tropical diseases, diabetes and cancer. In September 2010, Pfizer signed a technology transfer deal worth US\$735 million with Brazil's Ministry of Health, Israeli drugmaker Protalix and publicly funded domestic drugmaker Biomanguinhos. The deal enables Biomanguinhos to manufacture the drug taliglucerase alfa, a plant-based enzyme produced by a biological process, to treat the rare Gaucher's disease – yet another example of the growing interest in rare diseases (for more, see "A rare focus" on pages 54 and 55).

Government policy: fostering innovation

The Government of Brazil has actively promoted the nation's biotechnology industry with policies to encourage innovation. A case in point is the launch of the BrBiotec Brasil initiative in 2010.



BrBiotec's primary objective is to resolve conflicting interests among different stakeholders by fostering technical and business cooperation between companies, investors, teaching and research institutions, supporting agencies and government. The agency will also work toward creating alliances with international clusters.

Facilitating government policies have been instrumental in encouraging stem cell research in Brazil. Following the support it provided for the establishment of eight stem cell research laboratories in 2009 (see *Beyond borders*, 2010), the Brazilian Development Bank (BNDES) facilitated the launch of the Stem Cell Research Center of the National Cell Therapy Network (RNTC) in October 2010. The facility will develop technologies to cultivate and handle adult stem cells and will make them available to the RNTC for research.

In its effort to resolve conflicting regulations, the Government of Brazil has restricted the powers of the National Agency of Drugs and Medical Products (ANVISA) and granted the role of analyzing pharmaceutical intellectual property applications to the Institute of Intellectual Property (INPI). This is expected to help attract multinational companies looking to launch innovative patented drugs in Brazil. However, Brazil's regulatory system continues to receive criticism for the time it takes to process patent applications (around eight years), which is higher than in other emerging nations.

Japan: overcoming hurdles

Despite the makings of a promising industry – a strong history of innovative R&D, the world's second-largest pharmaceutical market, strong government support, pro-industry regulatory reforms – Japan's biotech market has yet to gain traction. The global financial crisis was a significant setback as investors in venture capital funds investing across all industries became extremely cautious. And as markets became more volatile, it was increasingly difficult for venture investors to exit investments.

Financing: a challenging environment

Just as the dust seemed to be settling on the financial crisis, Japan was hit by a devastating earthquake and tsunami in March 2011. Before these natural disasters, Japan's IPO market appeared to have turned a corner, with 22 IPOs completed across all industries in 2010. Four of the 22 IPOs were life sciences companies, including the blockbuster IPO by Otsuka Holdings, Japan's number two drugmaker by revenue behind top-ranked Takeda Pharmaceutical. Otsuka sold ¥198.6 billion (US\$2.5 billion) worth of shares in its oversubscribed IPO, making it the second-largest IPO for the year and the largest on record for the drug industry. Most of the money raised in the IPO has been earmarked for R&D as well as global expansion. Tokyo-based Cellseed was the lone biotech IPO in 2010, raising ¥2.07 billion (US\$25.8 million) in March 2010.

Also noteworthy on the investment front was an announcement by Innovation Network Corp. of Japan (INCJ) – a public-private investment fund launched in 2009 to promote innovation in Japan – that it plans to invest approximately ¥5 billion (US\$62 million) in Tokyo-based start-up Anaeropharma Science Inc. to develop a cancer drug. This is INCJ's first investment in a biotech company and many are watching and hoping that this will be the start of many more investments in Japan's cash-strapped industry.

Deals: Japanese pharma going global

Deals by Japanese biotechs were also limited in 2010. In contrast, Japan's pharma companies have been particularly active in transactions with foreign biotech firms as they seek to expand their geographic footprint, pipelines and product offerings. Astellas, Daiichi Sankyo, Eisai and Takeda have all been aggressively expanding their global reach in recent years. In 2010, Astellas closed the year's largest biotech acquisition when it purchased US-based OSI Pharmaceuticals for US\$4 billion in a transaction that started with a hostile bid but eventually turned friendly. In early 2011, Daiichi Sankyo acquired US-based biotech Plexxikon for approximately US\$935 million (including milestone payments). On the alliance front, Japan's Kyowa Hakko Kirin entered into a wide-ranging collaboration with US-based Dicerna Pharmaceuticals that has a potential value of more than US\$1 billion. The collaboration is focused on developing drugs in oncology, inflammation and immunology using Dicerna's proprietary RNAi technologies. And Fujifilm, defining medical-related business as a key growth

area, announced in August 2010 that it was entering into a capital partnership with Japan Tissue Engineering (also known as J-TEC) that gives Fujifilm a 41% equity in the company. J-TEC is a Japanese pioneer in regenerative medicine, and the alliance aims to accelerate the R&D of regenerative medicine materials.

Government: reforming the approval process

The Japanese government continues to focus on initiatives and reforms to help spur growth across the life sciences sector. One of the key areas of focus has been getting drugs to market faster. The Ministry of Health, Labor and Welfare will conclude its 5-Year Activation Plan in 2011, which was aimed at improving the infrastructure for conducting clinical trials. The intent was to enable Japan to more readily participate in global clinical trials and reduce "drug lag," the amount of time between a drug's approval in the EU or US and its approval in Japan. In addition to creating new incentives, implementation also focused on building a network of 10 national centers and 30 hub hospitals and strengthening their facilities for conducting advanced global trials. Japan's Pharmaceutical and Medical Devices Agency (PMDA) has also taken steps to improve review time for new drug applications, including increasing its reviewers (from about 200 in 2007 to more than 440 in 2010) and implementing electronic filing. By the end of 2011, the agency expects to meet its goal of a median review time of 12 months (9 months for priority products).

The biosimilars space in Japan is also developing some muscle. With the PMDA's introduction of a bioequivalence standard, Japan approved its first biosimilar – Sandoz's somatropin – in June 2009. Soon after, JCR Pharmaceuticals introduced a biosimilar for treating renal anemia in 2010. The focus has continued in 2011, with US-based Hospira announcing that it will start developing biosimilars through its subsidiary in Japan. In addition, Sawai Pharmaceutical has issued bonds with subscription rights to fund investments in biosimilar-related businesses, and Nichi-Iko Pharmaceuticals announced an alliance with South Korea's Arogen Inc. aimed at developing follow-on antibody drugs and other biosimilars.

Rebuilding and rebirth

As Japan begins to rebuild from this year's earthquake and tsunami, it is not yet apparent what the combined impact on the biotech industry will be – from loss of human capital and facilities and potentially reduced government, venture capital and public market funding. The IPO market is particularly vulnerable to economic uncertainty. Yet as we go to press, Japan's Parliament passed an emergency US\$48 billion budget for massive reconstruction and nations around the globe continue to lend their support. As Prime Minister Naoto Kan wrote in a 15 April *New York Times* editorial, perhaps "this difficult period will provide us with a precious window of opportunity to secure the 'Rebirth of Japan.'"

New Zealand: seeking sustainability

The New Zealand biotechnology market is slowly emerging from the global financial crisis with a sense of cautious optimism and a growing awareness of the impact of biotechnology across many industries and its importance to the economic, social and environmental future. Yet even though the angel investment community is active and follow-on funding is available for existing companies, there is a lack of more substantial funds for new ventures beyond the angel investor stage.

Asian investors: increased interest

One exception to this lack of funding is the increased interest in New Zealand by Asian investors. Increasingly, the direction of New Zealand biotechnology will be shaped by the country's ability to cater to the needs of emerging markets, including China. This was demonstrated by the US\$18 million investment by Chinese venture capitalists in Lanzatech, a company developing a method to convert industrial waste gasses into ethanol. Japanese interests were also active, investing in Living Cell Technology, a company using encapsulated porcine islets to treat people with insulin-dependent diabetes.

New Zealand's free trade agreement with China has in part paved the way for wider investment in biotechnology, especially in core

agricultural activities and food-related biotech, with an expectation for high growth in the coming years. Sustainable biotechnology also offers solutions to increased productivity and sustainable land management, both of which are of paramount importance to a nation looking to maximize land productivity at a time of heightened awareness of the environmental and financial impact of climate change.

Government: seeking sustainability

The government continues to invest in science and to emphasize the importance of biotechnology as a key component of its economic growth agenda. The 2010 budget identified research, science and technology as drivers of economic growth, and, as part of a larger allocation, included \$20 million for trial technology transfer vouchers intended to encourage links between companies and publicly funded research organizations. High on the government's agenda is the desire to mitigate some of the pastoral industry's environmental impact through biotechnology, which led to the launch of the Agricultural Greenhouse Gas Research Centre. The government-funded center has been set up to research ways to reduce greenhouse gas emissions without reducing agricultural output. The largest wastewater algae to bio-crude oil demonstration project in the world was also opened during 2010 at the Christchurch Wastewater Treatment Plant, combining bio-crude oil conversion technology from Solray with scientific expertise from the National Institute of Water and Atmospheric Research on advanced wastewater treatment and algal production pond technology.

A new Ministry of Science and Innovation was created by merging the Ministry of Research, Science and Technology and the Foundation for Research, Science and Technology. The new ministry will provide a focal point for government initiatives in this sector, including managing science funding, advising the government on New Zealand's science system and, importantly, driving the knowledge transfer from the science sector to business and other research users.



Singapore: biotech destination

Ranked globally as the easiest country in which to conduct business, with strong intellectual property protection, Singapore continues to grow its biotechnology industry. The country maintains its status as the preferred biomedical research and manufacturing destination for multinational companies due to its strategic location, modern infrastructure, favorable regulatory framework and quality workforce. However, lack of funding for domestic, innovation-based start-up companies persists.

Innovation: gathering pace

Driven by the research efforts of more than 5,000 researchers from its public sector institutes, Singapore has momentum in developing new innovation. In 2010, Singapore established the Biomedical Sciences Industry Partnership Office to serve as a conduit between multinational companies and research professionals at Singapore's academic and public institutions. The goal is to facilitate the translation of scientific concepts into viable therapies via public-private partnerships. Singapore has also taken significant strides in stem cell research, with discoveries of alternative methods to generate stem cells. To give impetus to stem cell research, the Bioethics Advisory Committee has recommended the establishment of a national body to review and monitor stem cell research in the country.

CROs: following the multinational route

The 2009 and 2010 editions of *Beyond borders* highlighted the trend of manufacturing and pure research firms establishing operations in Singapore. However, over the past year, the country's growth opportunities have also attracted clinical research organizations (CROs) focused on biotechnology products. US-based PPD Inc. has established a joint venture, BioDuro Biologics, with Taijitu Biologics Ltd. to focus on the discovery of novel biotherapeutics. This venture has enhanced PPD's capability to deliver drug discovery services for biopharmaceutical companies on a global basis. Similarly, PAREXEL, another US-based CRO, has opened two new clinical logistics services facilities in Singapore to support its clients in effectively managing their global clinical trial supply requirements.



Funding: an ongoing endeavor

The Government of Singapore is expected to spend S\$16.1 billion (US\$12.5 billion) on research innovation in the sector over the next five years – a 20% increase over the previous budget. Of the total allocation, the Government plans to invest S\$3.7 billion (US\$2.87 billion) in biomedical sciences research, an increase of 12% over 2006-2010. However, the sector continues to struggle to obtain funding from venture capitalists for pre-commercial research stage companies, due to the lack of exit routes for these companies via public offerings. ►

Turning the corner



Industry performance

Turning the corner

Growth in established biotechnology centers, 2009-10 (US\$b)

	2010	2009	% change
Public company data			
Revenues	84.6	78.3	8%
R&D expense	22.8	22.3	2%
Net income (loss)	4.7	3.6	30%
Number of employees	178,750	172,690	4%
Number of companies			
Public companies	622	622	0%

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

The big picture

While the global financial crisis began in late 2008, it was not until last year – in our 2010 report, the first to feature an entire year of post-crisis numbers – that we got a comprehensive view of the downturn’s toll on the biotechnology industry’s financial performance. That report revealed that, despite the global economy being mired in a historic recession, the industry’s revenue growth held up well (after normalizing for Roche’s acquisition of Genentech, which removed one of the world’s largest biotech companies from the biotech numbers). The strong showing on the top line was not surprising, since the sector’s revenues come from a relatively small group of companies that were largely unscathed by the downturn. To understand the real impact of the crisis, it was necessary to look lower down on the income statement – to R&D expense and net income – where the travails of smaller companies had a palpable impact on the industry’s performance. In each of the four established biotechnology centers – the US, Europe, Canada and Australia – large numbers of firms undertook drastic cost-cutting measures to survive. These efforts resulted in a much

stronger bottom line, propelling a sector that has bled red ink for most of its history to unprecedented levels of aggregate profitability. But while the focus on operating efficiency has its benefits, it has come at a high cost. In an industry where R&D is by far the biggest expenditure, it was inevitable that deep spending cuts would lead companies to slash R&D expenditures. Indeed, the industry’s R&D spending across the established biotechnology centers fell by 21% in 2009 – the only time R&D spending has decreased in the industry’s history. In an innovation-driven industry, it is hard not to be concerned about what the longer-term impacts on the pipeline will be from these cuts.

A year later, the picture has improved considerably. The industry appears to have turned the corner, though it has not returned to pre-crisis levels of normalcy. Across the established biotech centers, revenues grew by 8% – identical to growth in 2009 after adjusting for the Genentech acquisition, but well below the 12% seen in 2008 or the high double-digit growth rates the industry was able to deliver in many prior years. R&D expenditures, which had plummeted by 21% in 2009,



grew by a modest 2% in 2010 – a positive development, but far below the investments that biotech companies have historically made in innovation. In 2009, 64% of US companies and 55% of European companies decreased their R&D spend; in 2010, those numbers fell to 49% and 45%, respectively. In another sign of stabilization, the number of public companies – which fell by 11% in 2009 amid a widespread culling of struggling firms – stayed flat in 2010. Lastly, the bottom line picture continued to improve in what remains a very cost-conscious environment. Net income grew by 30%, from US\$3.6 billion in 2009 to US\$4.7 billion in 2010 – an all-time record.

The question all of this raises is whether this is the shape of things to come – will the biotech industry return to higher revenue and R&D growth numbers, or is this year's performance typical of what we might reasonably expect going forward? In "The new normal," last year's *Introduction* article, we asked whether the industry's recovery from the financial crisis would see it return to the state of affairs it has long known, or whether the industry would instead settle in on a "new normal," with funding and performance below the heights achieved during the easy-money years that preceded the financial crisis. The reality,

Ernst & Young survival index, 2009-10

	US		Europe		Canada	
	2010	2009	2010	2009	2010	2009
More than 5 years of cash	33%	30%	41%	45%	26%	22%
3-5 years of cash	6%	8%	6%	11%	11%	5%
2-3 years of cash	12%	8%	10%	7%	14%	5%
1-2 years of cash	23%	18%	15%	12%	14%	17%
Less than 1 year of cash	26%	36%	28%	25%	35%	51%

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

however, is that biotech has always existed in two realities – one for the haves and the other for the have-nots – and what we are now seeing is the emergence of two new normals. The fallout from the financial crisis is disproportionately affecting the have-nots, where access to capital remains challenging and R&D spending remains depressed relative to pre-crisis levels. For more mature companies, on the other hand, the new normal is being defined not so much by the aftermath of the financial crisis as by other trends: a world of growing pricing pressures, comparative effectiveness research and regulators that have become inordinately risk-averse on matters of product safety. Pendulums tend to swing back, and all of these pressures will ease with the passage of time. But for

the immediate future, we do not expect any major reversals of these trends, and the outlook may indeed be more of the same. As mature companies continue to face higher scrutiny of their products' safety and efficacy, they are likely to deliver solid revenue growth in the high single-digit or low double-digit range (but below the higher growth rates achieved in the first half of the 2000s). And as long as tight funding remains an inescapable part of the new normal for emerging companies, R&D spending will remain under pressure. Numbers such as the ones we have seen in 2010 – steady, solidly profitable, but slow-growing – may indeed be the shape of things to come over the next few years.

United States

US biotechnology at a glance, 2009-10 (US\$b)

	2010	2009	% change
Public company data			
Product sales	52.6	48.1	9%
Revenues	61.6	56.2	10%
R&D expense	17.6	17.1	3%
Net income	4.9	3.7	33%
Market capitalization	292.0	271.6	8%
Number of employees	112,200	106,600	5%
Financings			
Capital raised by public companies	16.3	13.5	21%
Number of IPOs	15	3	400%
Capital raised by private companies	4.4	4.6	-3.2%
Number of companies			
Public companies	315	314	0.3%
Private companies	1,411	1,389	2%
Public and private companies	1,726	1,703	1%

Source: Ernst & Young

Data were generally derived from year-end information (31 December). The 2010 data are estimates based on January-September quarterly filings and preliminary annual financial performance data for some companies. The 2009 estimates have been revised for compatibility with 2010 data. Numbers may appear inconsistent because of rounding.

In the US, the revenues of publicly traded biotech companies grew to US\$61.6 billion – a 10% increase, identical to the 2009 growth rate (after adjusting for the Genentech acquisition). In a sign of stabilization, R&D expense held steady with a modest 3% increase – a noteworthy improvement after a sharp 13% decline in 2009 (after adjusting for Genentech). And, in what remains a very cost-conscious environment, US public companies added US\$1.2 billion to their collective bottom line, as net income grew by 33% to reach US\$4.9 billion. The number of companies held steady and employees grew by 5% – a significant change from 2009, when both indicators declined as many companies restructured to survive and a number of others ceased operations altogether.

US biotechnology: commercial leaders and other companies (US\$b)

	2010	2009	US\$ change	% change
Commercial leaders				
Revenues	48.6	44.8	3.9	9%
R&D expense	8.8	8.2	0.6	7%
Net income	11.2	10.3	0.9	9%
Market capitalization	179.6	179.6	0.0	0%
Number of employees	74,230	72,580	1,650	2%
Other companies				
Revenues	13.0	11.5	1.5	13%
R&D expense	8.7	8.9	(0.1)	-1%
Net income (loss)	(6.3)	(6.6)	0.3	-4%
Market capitalization	112.4	91.9	20.5	22%
Number of employees	38,000	37,790	210	1%

Source: Ernst & Young

"Commercial leaders" are defined as companies with 2009 revenues in excess of US\$500 million. Data were generally derived from year-end information (31 December). The 2010 data are estimates based on January-September quarterly filings and preliminary annual financial performance data for some companies. The 2009 estimates have been revised for compatibility with 2010 data. Numbers may appear inconsistent because of rounding.

As discussed in "The big picture," above, to obtain an accurate understanding of the biotechnology industry's performance, one needs to examine the performance of mature commercial companies relative to the rest of the industry – all the more so at a time when a major economic downturn has affected the two groups in very different ways. In this year's report, we have conducted such an analysis, defining "commercial leaders" as the 13 companies that had 2009 revenues exceeding US\$500 million. (The story is very similar regardless of the threshold used.)

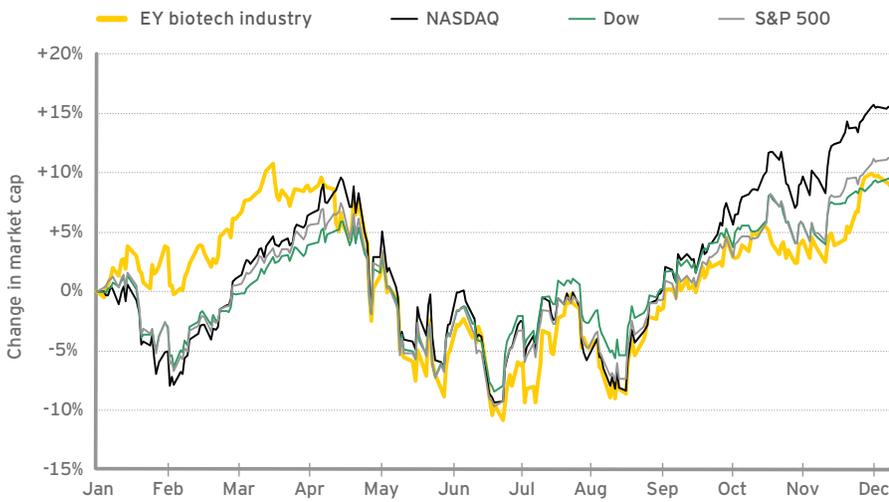
With respect to the top and bottom lines, the two groups turned in a fairly similar performance: robust revenue growth and continued improvements on the bottom line. While the commercial leaders accounted for 72% of the US industry's revenue growth in 2010, the other companies had a higher growth rate in percentage terms – 13%, compared to 9% for

the commercial leaders. And while the two groups are in very different situations with respect to net income (the commercial leaders are solidly in the black; the other companies firmly in the red), both groups were able to improve their collective bottom lines in 2010.

On R&D expense, however, the story is dramatically different for the two groups. The commercial leaders increased R&D spending by 7% during the year, while the other companies cut R&D by 1%. The brunt of the industry's R&D cuts, in other words, is being borne by emerging companies – precisely the segment that has historically been a crucial source of innovation.

The market capitalization of the two groups of companies performed very differently during the year – something that is discussed further in the next set of charts.

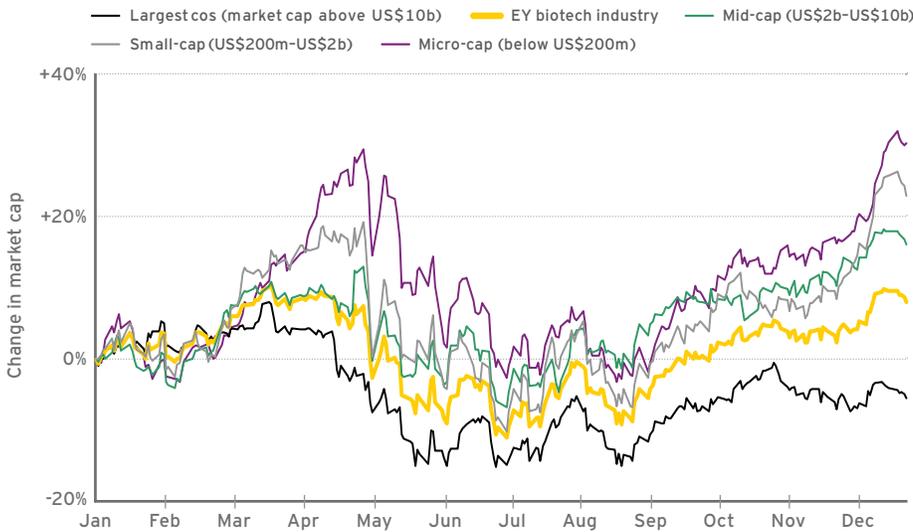
In 2010, the biotech industry slightly underperformed the market ...



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.

The market capitalization of the US biotech industry slightly underperformed leading stock market indices during the year. However, the largest companies significantly trailed the overall sector, while mid-, small- and micro-cap companies did markedly better than average.

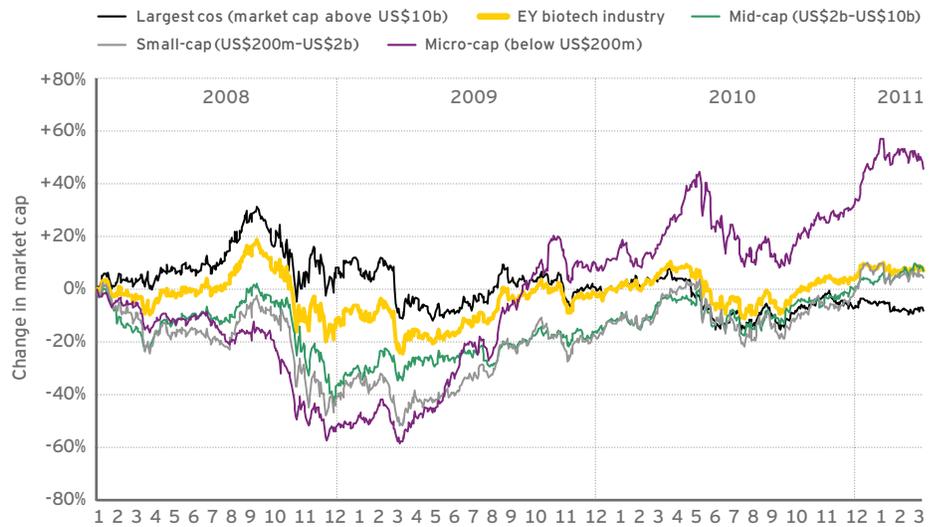
... with smaller companies continuing to outperform large ones



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.

To put these numbers in context, it is helpful to look at them over a longer time frame. In 2008, the largest companies significantly outperformed the other segments. When the downturn hit, this group was the least affected, as investors fled smaller stocks that were perceived as being more risky. As market confidence rebounded, the spread between the different segments narrowed, and over time, the micro-caps have more than made up the lost ground.

After declining in 2008, smaller companies more than recovered ground



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.



US companies with revenues greater than US\$500 million

2007 15 companies	2008 13 companies	2009 13 companies	2010 16 companies
			Organic growth → Alexion
Amgen	Amgen	Amgen	Amgen
Amylin	Amylin	Amylin	Amylin
Applied Biosystems	Acquired by Life Technologies		
Biogen Idec	Biogen Idec	Biogen Idec	Biogen Idec
Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories
Celgene	Celgene	Celgene	Celgene
Cephalon	Cephalon	Cephalon	Cephalon
		Organic growth → Cubist	Cubist
			Organic growth → Gen-Probe
Genentech	Genentech	Acquired by Roche	
Genzyme	Genzyme	Genzyme	Genzyme
Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences
Organic growth →	Illumina	Illumina	Illumina
Imclone	Acquired by Lilly		
Invitrogen	Life Technologies (name change)	Life Technologies	Life Technologies
Sepracor	Sepracor	Acquired by Dainippon Sumitomo	
IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories
Millennium Pharmaceuticals	Acquired by Takeda		
		IPO → Talecris Biotherapeutics	Talecris Biotherapeutics
			Organic growth → United Therapeutics

Source: Ernst & Young, company financial statements

It is important to note that biotechnology has always been a dynamically changing industry. This chart lists US public companies in each of the last four years that could be classified as “commercial leaders” based on the US\$500 million threshold used earlier. While there is a constant core group of very large and mature companies, a number of other firms have been dropped from the list due to acquisitions. In 2011, another large and tremendously successful biotech, Genzyme, will disappear from this list as it is acquired by Sanofi.

In that context, it is heartening to note that biotech still retains the ability to replenish those losses with new generations of leaders. In 2010 alone, three companies grew large enough to be added to the list of commercial leaders.

Large companies remain on the lookout for companies to acquire, and we expect to see more activity on the M&A front over the next year. While we cannot predict which firms will get purchased, many of the names on this list are often speculated about as likely takeout targets – or acquirers.

The hunters and hunted?

US drug development biotech companies by market cap

Market cap more than US\$10b

Company	Revenues (US\$b)
Amgen	15.1
Biogen Idec	4.7
Celgene	3.6
Gilead Sciences	7.9

Market cap US\$1b-US\$5b

Company	Revenues (US\$m)
Alkermes	178
Amylin Pharmaceuticals	669
Amyris Biotechnologies	80
Auxilium	211
BioMarin	376
Cubist Pharmaceuticals	637
Dendreon	48
Exelixis	185
Incyte Corporation	170
InterMune	259
Ironwood Pharmaceuticals	46
Jazz Pharmaceuticals	174
Myriad Genetics	363
Nektar Therapeutics	159
Onyx Pharmaceuticals	325
Opko Health	37
Pharmasset	1
Regeneron	459
Salix Pharmaceuticals	337
Seattle Genetics	108
Theravance	24
United Therapeutics	604
ViroPharma	439

Market cap US\$5b-US\$10b

Company	Revenues (US\$m)
Alexion Pharmaceuticals	541
Human Genome Sciences	157
Vertex Pharmaceuticals	143

Source: Ernst & Young and company financial statement data

Selected 2010 US biotechnology public company financial highlights by geographic area (US\$m, % change over 2009)

Region	Number of public companies	Market capitalization 31.12.2010	Revenues	R&D	Net income (loss)	Cash and equivalents	Total assets
San Francisco Bay Area	65 8%	58,617 -2%	13,522 16%	3,592 6%	1,952 63%	4,439 15%	23,894 17%
New England	45 -2%	63,619 22%	12,393 7%	4,229 4%	202 -21%	4,375 40%	27,710 5%
San Diego	35 0%	31,498 33%	6,342 10%	1,586 -1%	(423) -25%	2,414 34%	17,026 7%
New Jersey	23 0%	32,565 13%	4,305 25%	1,491 20%	621 72%	2,209 49%	11,724 77%
New York State	23 0%	6,442 -4%	984 -21%	688 -6%	(495) 72%	360 -46%	2,136 -30%
Southeast	19 6%	2,919 26%	313 36%	228 13%	(213) 1%	275 -17%	727 0%
Mid-Atlantic	18 -5%	11,341 2%	1,400 12%	663 2%	(251) 189%	833 -33%	4,788 6%
Pennsylvania/Delaware Valley	14 17%	9,731 15%	3,772 34%	760 7%	322 -679%	2,239 -18%	7,218 3%
Pacific Northwest	13 -19%	7,678 20%	209 -27%	365 -19%	(754) 27%	256 -67%	1,252 -32%
Los Angeles/Orange County	13 -13%	53,830 -11%	15,321 1%	3,137 -4%	4,292 4%	3,531 7%	44,181 7%
North Carolina	12 9%	7,885 42%	2,240 12%	335 1%	82 237%	1,090 105%	3,232 20%
Midwest	10 0%	689 27%	35 29%	107 36%	(168) 17%	125 -12%	179 -9%
Texas	9 0%	1,387 25%	148 12%	112 -15%	(103) -26%	154 -24%	654 26%
Colorado	7 17%	719 -11%	107 205%	110 -16%	(154) -24%	100 -60%	269 -22%
Utah	3 0%	2,743 -2%	467 7%	111 3%	62 48%	159 44%	962 10%
Other	6 -25%	364 -31%	90 -8%	47 -6%	(42) 298%	42 41%	230 -6%
Total	315 0%	292,027 8%	61,648 10%	17,562 3%	4,930 33%	22,600 10%	146,180 10%

Source: Ernst & Young and company financial statement data
Percent changes refer to change over December 2009. 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

A closer look

New reporting requirements for payments to health care professionals



Diana Hoff
Partner
Ernst & Young LLP

The regulatory environment for companies commercializing pharmaceuticals in the US is requiring increased transparency for payments and other “items of value” provided to health care professionals (HCPs) and health care organizations (HCOs). The current and anticipated regulations will require organizations to disclose payments and items of value made directly or indirectly to US-based physicians and related entities. Examples of payments and items of value include speaker fees, meals, education materials, and travel expenses for a US physician to present at a conference. Planning to capture and report all such payments can be a complex endeavor requiring organizations to design new processes and build technical solutions to address regulatory and corporate transparency requirements, as well as build in the flexibility and capability to meet future requirements. Global organizations require the creation of a solution that is applicable across global systems and operations. And lastly, the impacts of aggregate spend are not restricted to internal audiences and regulators but also reach a large external audience that includes physicians, nurses, medical researchers and the general public.

As companies have begun to address the regulations, certain key challenges have been identified, including:

- ▶ Reaching a common definition for HCP/HCO that spans federal and state legislation
- ▶ Anticipating the impacts and reactions from external stakeholders, including clients and suppliers
- ▶ Capturing HCP spend data in a single location to allow integrated reporting
- ▶ Adhering to evolving federal and state reporting requirements and anticipating emerging global requirements and impacts on business practices

While some have viewed these requirements as a matter of data collection and reporting, leading companies at the forefront of adoption have approached the issue in an integrated way, considering people, process and technology implications. This includes acknowledging that both clinical and commercial systems will be affected and that engagement of key business resources in those units will be necessary.

A closer look

VAT and customs – a hidden cost in global clinical trials



Howard W. Lambert
Senior Manager
Ernst & Young LLP

Clinical trials are becoming increasingly global as companies seek more rapid patient enrollment and cost advantages. Frequently, trials are conducted in countries where a biotech company does not have a presence, which could limit the ability to receive a refund of any value-added tax (VAT) incurred on the value of the drug imported for the trial and on the services performed under the study. With VAT rates ranging from 10%-20% on top of customs and duty rates, this could represent a significant hidden cost of conducting the trial.

Once a biotech company has settled on the optimal mix of locations, the company will need to carefully consider the contractual terms with a clinical research organization (CRO). In particular:

- ▶ Who will be the importer of record (IOR) for the products to be tested?
- ▶ If the biotech company cannot act as the IOR, could the IOR be the CRO?
- ▶ If the imported products are dutiable, are there free trade agreements or other special programs that provide relief (e.g., inward processing, free trade zones and temporary admission)?

- ▶ Are the imports of the products to be tested subject to other regulations (e.g., by the FDA or equivalent body) that may require specific conditions to be met before a product can be imported into a particular country?
- ▶ How can the value of the import be determined in cases where it is not a normal sale of goods?
- ▶ Are import VAT reliefs available (e.g., on samples)?
- ▶ If VAT is charged on imported products and services provided, under what conditions, if any, will the company be able to get a refund?

VAT and customs costs can add an unexpected, and at times significant, cost to a global clinical trial. Biotech companies and their CRO partners already invest significant time and effort in designing and optimizing global clinical trials. In addition, it is prudent to explore these indirect tax issues before launching trials.

Europe

The performance of Europe's publicly traded biotech companies was remarkably similar to that of their US counterparts – signaling that biotech companies face remarkably similar market forces and challenges in today's business climate. The top line grew by 12%, besting the 8% growth recorded in 2009 and two percentage points ahead of the US. R&D expense, which had decreased by 2% in 2009, came back with a modest 5% increase in 2010. And, as in the US, the bottom line improved for the second year in a row.

European biotechnology at a glance, 2009-10 (€m)

	2010	2009	% change
Public company data			
Revenues	13,004	11,606	12%
R&D expense	3,400	3,229	5%
Net income (loss)	(459)	(467)	-2%
Market capitalization	59,433	47,420	25%
Number of employees	49,060	48,660	1%
Financings			
Capital raised by public companies	1,862	2,091	-11%
Number of IPOs	10	3	233%
Capital raised by private companies	1,021	790	29%
Number of companies			
Public companies	172	167	2%
Private companies	1,662	1,675	-1%
Public and private companies	1,834	1,842	-0.5%

Source: Ernst & Young

Data were generally derived from year-end information (31 December). The 2010 data are estimates based on January-September quarterly filings and preliminary annual financial performance data for some companies. The 2009 estimates have been revised for compatibility with 2010 data. Numbers may appear inconsistent because of rounding.

The analysis of commercial leaders and other companies also showed some similarities to the US – as well as some notable differences. Using a threshold of €500 million to demarcate the two groups, we found that both segments recorded strong revenue growth. Notably, both groups also increased R&D expense, though R&D grew at a higher rate for the commercial leaders. But, unlike the US, net income increased for the commercial leaders, while the other companies moved deeper into the red.

European biotechnology: commercial leaders and other companies (€m)

	2010	2009	€ change	% change
Commercial leaders				
Revenues	9,845	8,784	1,062	12%
R&D expense	1,586	1,478	108	7%
Net income (loss)	1,079	993	86	9%
Market capitalization	36,761	29,253	7,508	26%
Number of employees	30,970	29,950	(1,020)	3%
Other companies				
Revenues	3,158	2,822	336	12%
R&D expense	1,814	1,751	63	4%
Net income (loss)	(1,538)	(1,460)	(78)	5%
Market capitalization	22,672	18,167	4,505	25%
Number of employees	18,090	18,710	(620)	-3%

Source: Ernst & Young

"Commercial leaders" are defined as companies with 2009 revenues in excess of €500 million. Data were generally derived from year-end information (31 December). The 2010 data are estimates based on January-September quarterly filings and preliminary annual financial performance data for some companies. The 2009 estimates have been revised for compatibility with 2010 data. Numbers may appear inconsistent because of rounding.

The hunters and hunted? EU companies by market cap

Market cap over €10b

Company	Country	Revenues (€m)
Shire	UK	2,620

Market cap €5b-€10b

Company	Country	Revenues (€m)
Novozymes	Denmark	1,306

Market cap €1b-€5b

Company	Country	Revenues (€m)
Actelion	Switzerland	1,398
Amarin Corporation	Ireland	0
Biocompatibles International	UK	40
BTG	UK	115
Elan Corporation	Ireland	636
Ipsen	France	1,170
Meda	Sweden	1,214
Qiagen	Netherlands	821

Source: Ernst & Young, CapIQ

Given the different size composition of Europe's industry, it has relatively fewer potential "hunters." Of course, European big pharma companies, which are not on this list, remain active buyers.

European micro-cap stocks outperformed the other biotech companies

— Largest cos (market cap above €2.5b) — EY biotech industry — Mid-cap (€1b-€2.5b)
 — Small-cap (€200m-€2b) — Micro-cap (below €200m)



Source: Ernst & Young, finance.yahoo.com

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

In another similarity with the US, European micro-cap stocks outperformed other size segments in 2009 and 2010.

Selected 2010 European biotechnology public company financial highlights by country (€m, % change over 2009)

Country	Number of public companies	Market capitalization 31.12.2010	Revenues	R&D	Net income (loss)	Cash and equivalents	Total assets
United Kingdom	41 -13%	16,307 62%	3,298 14%	819 6%	282 74%	847 -1%	5,739 13%
France	23 28%	6,135 -8%	2,302 7%	466 8%	(11) -257%	483 -11%	3,622 11%
Sweden	22 10%	4,804 15%	1,730 6%	231 -5%	2 -98%	271 62%	5,029 25%
Israel	18 20%	1,352 4%	67 114%	77 16%	(103) 15%	137 -9%	319 28%
Denmark	10 11%	8,305 51%	1,478 18%	388 -5%	12 -108%	413 30%	2,647 14%
Germany	14 -7%	1,523 10%	165 -26%	165 5%	(121) -16%	221 11%	826 10%
Switzerland	10 0%	5,681 11%	1,531 24%	441 7%	276 714%	1,097 38%	2,614 19%
Norway	8 14%	1,161 86%	73 263%	45 42%	(29) 222%	193 30%	254 39%
Netherlands	7 0%	5,723 -8%	1,299 8%	252 22%	14 -81%	914 -9%	4,173 3%
Belgium	6 -14%	1,561 18%	200 22%	180 17%	(65) -22%	210 -37%	581 -7%
Other	13 0%	6,880 36%	862 9%	336 -2%	(718) 89%	473 -40%	2,483 -14%
Total	172 2%	59,433 25%	13,004 12%	3,400 5%	(459) -2%	5,259 2%	28,287 10%

Source: Ernst & Young and company financial statement data
Percent changes refer to change over December 2009. Some numbers may appear inconsistent because of rounding.



Canada

The financial performance of the Canadian biotech industry was overshadowed by the Valeant/Biovail merger, which effectively removed the largest Canadian firm from the domestic industry. In 2009, Biovail had accounted for almost 40% of the Canadian industry's revenues.

Revenues of Canadian publicly traded biotech companies fell by 38% in 2010, largely as a result of the Valeant acquisition. Normalizing the numbers for this deal (by removing Biovail from both the 2009 and 2010 results), the "apples-to-apples" growth in revenues would have been about 1% – essentially flat. R&D expenditures fell for the second year in a row, as companies focused on operating efficiency, and the decline was exacerbated by the Valeant/Biovail transaction. R&D expenditures fell by 21% in 2010. Net loss deteriorated, from US\$11 million to US\$336 million.

Canadian biotechnology at a glance, 2009-10 (US\$m)

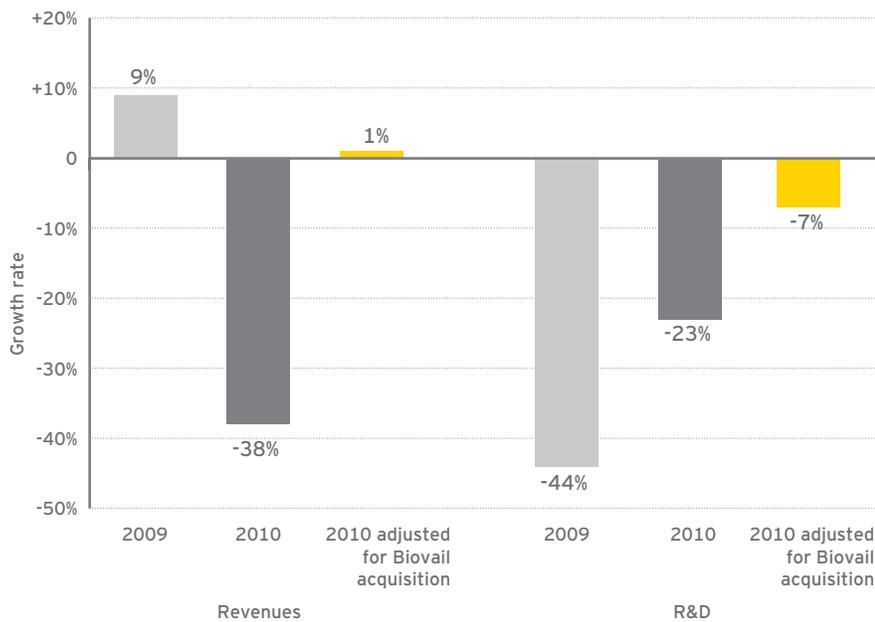
	2010	2009	% change
Public company data			
Revenues	1,308	2,110	-38%
R&D expense	222	287	-23%
Net income (loss)	(336)	(11)	3,029%
Market capitalization	5,176	6,782	-24%
Number of employees	4,870	6,370	-24%
Financings			
Public company financings	396	633	-38%
Number of IPOs	0	0	0%
Private company financings	87	100	-13%
Number of companies			
Public companies	63	67	-6%
Private companies	230	260	-12%
Public and private companies	293	327	-10%

Source: Ernst & Young

Financial data for 2009 were converted to US\$ using an exchange rate of 1.03 (C\$ per US\$), except market capitalization, which was converted using an exchange rate of 1.01. Data for 2009 were converted to US\$ using an exchange rate of 1.14, except market capitalization, which was converted using an exchange rate of 1.05. Data for 2009 have been restated to reflect full-year results, since estimates in *Beyond borders* 2010 included some estimation of fourth-quarter results. Numbers may appear inconsistent because of rounding.



Behind the numbers: the impact of the Biovail acquisition on Canadian biotech financial results



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

It is encouraging that the R&D expenses of companies other than Biovail declined by only 7% in 2010. In 2009, the same group of companies had slashed R&D by an astounding 56%, and the R&D expenses of the overall industry (i.e., including Biovail) declined by 44% – by far the largest percentage fall that year in the major biotech markets we track.

However, the revenues of companies other than Biovail were essentially stagnant in 2010. This stands in stark contrast to 2009, when revenues of the entire industry increased by 9% (and revenues of companies other than Biovail increased by 10%), even amid the economic downturn.



Australia



Australian biotechnology at a glance, 2009-10 (US\$m)

Public company data	2010	2009	% change
Revenues	4,371	3,731	17%
R&D expense	482	416	16%
Net income (loss)	681	542	26%
Number of employees	12,620	11,060	14%
Market capitalization	21,556	18,659	16%
Total assets	6,142	7,159	-14%
Number of public companies	72	74	-3%

Source: Ernst & Young and company financial statement data

As in 2009, the Australian sector's financial performance was at least partly colored by exchange rate fluctuations. The Australian dollar, which had declined by about 16% in 2009, essentially regained the ground it had ceded in 2010. Consequently, the results of Australian public companies look much healthier when converted into US dollars than when stated, as reported by Australian companies, in Australian dollars. The industry's revenues grew by 17% in US dollars, but they were essentially flat in Australian dollars. And while Australia appears to be bucking the trend seen in other established clusters by increasing R&D spending, the reality is that the industry's R&D spending actually declined by 2% when measured in Australian dollars. As in the US and Europe, the bottom line continued to improve, as the Australian sector moved more firmly into the black, growing net income by 26% (or 6% in US dollars).

While CSL continues to dominate the Australian sector, more companies appear to be maturing and contributing to the sector's top- and bottom-line growth. Examples include Biota, HalcyGen Pharmaceuticals, Acrux and Cellestis. ►

A rare focus: the legacy of a pioneer

The ranks of big biotech continue to thin. In recent years, several of the industry's most successful firms – Chiron, Genentech, MedImmune, Millennium, Serono and others – have been acquired by non-biotech buyers. Now, with the acquisition of Genzyme by Sanofi, another biotech leader is poised to disappear into the embrace of a big pharma buyer.

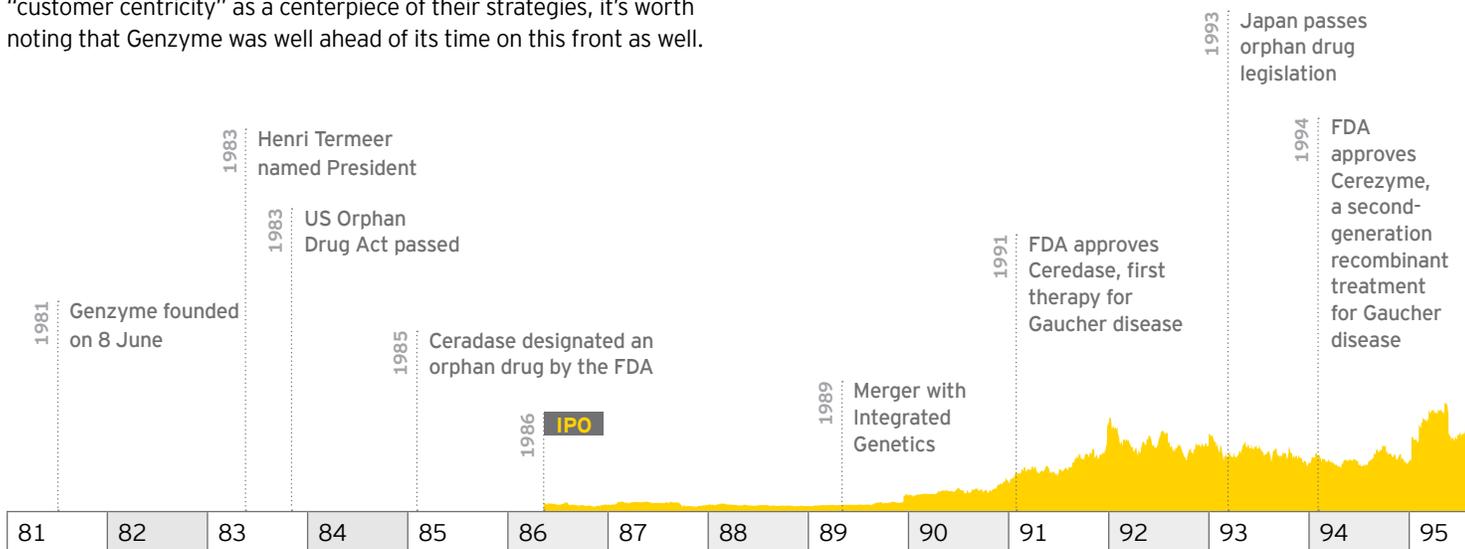
From its founding 30 years ago during biotech's earliest days, Genzyme grew into a multibillion-dollar global enterprise. In 2010, it earned more than US\$4 billion in revenues and employed more than 10,000 individuals. Its alumni have gone on to start and run scores of other firms – creating a multiplier effect that continues to ripple across the industry.

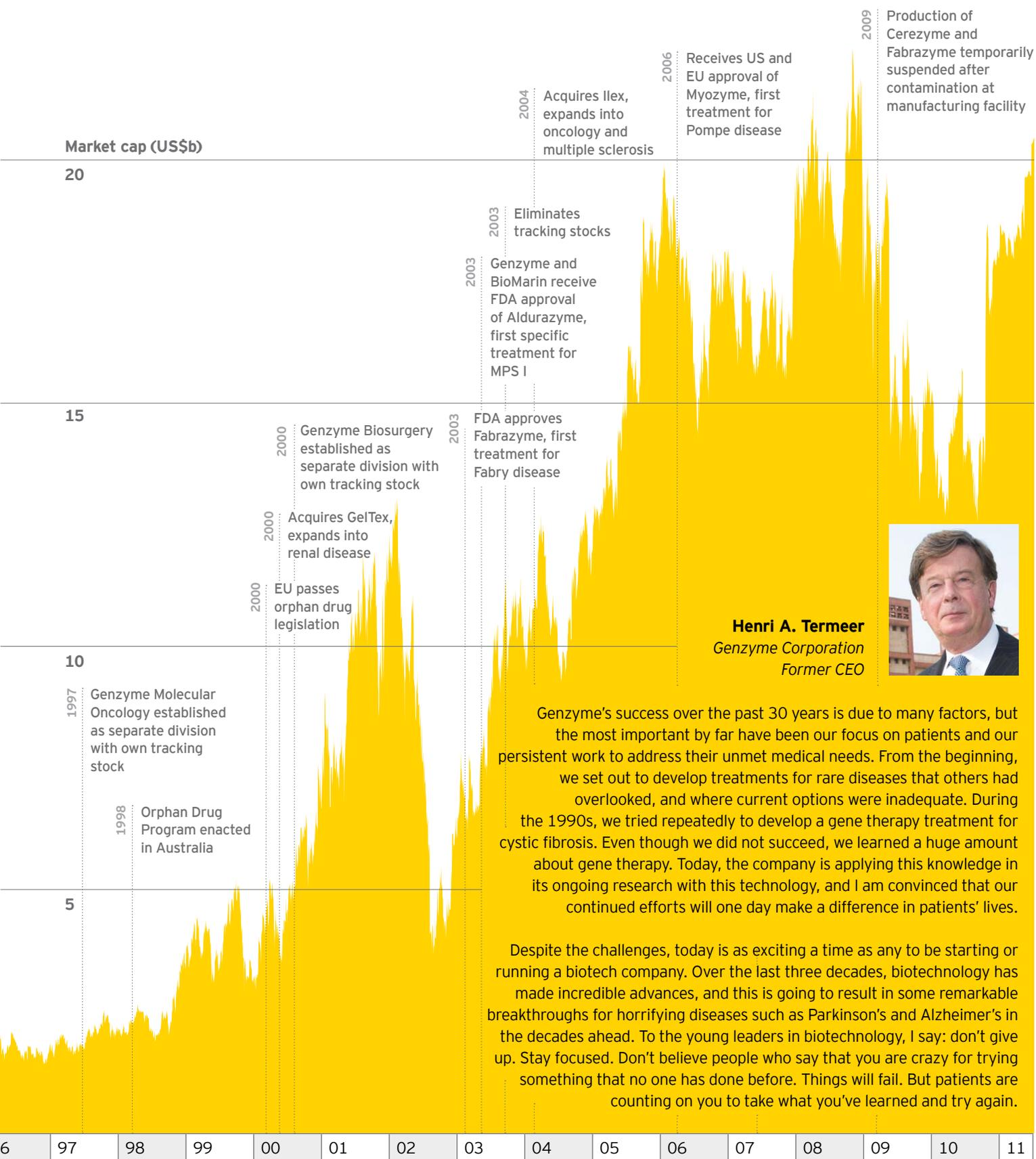
Yet Genzyme's vast legacy cannot be fully measured using the usual financial metrics. Its biggest contribution is arguably its pioneering focus on rare diseases, which proved that there was a viable business model in developing treatments for conditions with very small patient populations. While the passage of orphan drug legislation in the US and other key markets provided important economic incentives, it was Genzyme that demonstrated that this was a sustainable business.

Today, more than 60 companies around the world are predominantly focused on rare diseases (see accompanying table). Even big pharma companies – the architects of the blockbuster model – are increasingly moving into the space. (For more, refer to the interview with Mark Fishman of Novartis, as well as the *Introduction* article.) And in an era when companies are adopting "customer centricity" as a centerpiece of their strategies, it's worth noting that Genzyme was well ahead of its time on this front as well.

Orphans no more? Companies with a major focus on rare diseases		
Adienne	Edison Pharmaceuticals	Pharming
Advanced Cell Technology	Eleison Pharmaceuticals	PolarisRx
AesRx	Enobia Pharma	Protalix Biotherapeutics
AGI Therapeutics	ERYtech Pharma	QOL Medical
Alaxia	FerroKin	Rare Disease Therapeutics
Alexion Pharmaceuticals	Fresenius Biotech	Recordati
Amicus Therapeutics	Gentium	Regeneron Pharmaceuticals
AMT	Hy BioPharma	Santhera Pharmaceuticals
AOP Orphan	Ikaria	Shire
Atlantic Healthcare	Innate Pharma	Sigma-Tau Pharmaceuticals
AVI BioPharma	JCR Pharmaceuticals	Swedish Orphan Biovitrum
BioMarin Pharmaceuticals	Lantibio	Symphogen
Bioniche Life Sciences	LFB	Synageva BioPharma
BL&H	Lundbeck	TheraQuest Biosciences
BlackSwan Pharma	mondoBIOTECH	Tzamal Medical
Bone Therapeutics	Nobelpharma	Viropharma
CSL Behring	Oncoscience	Vivendy Therapeutics
Diamyd Medical	Orfagen	Zacharon Pharmaceuticals
Dompe	Orphan Therapeutics	Zymenex
DuoCort	OxThera	
Edimer Pharmaceuticals	Paladin Labs	

Source: Ernst & Young, company disclosures





Henri A. Termeer
Genzyme Corporation
Former CEO



Genzyme's success over the past 30 years is due to many factors, but the most important by far have been our focus on patients and our persistent work to address their unmet medical needs. From the beginning, we set out to develop treatments for rare diseases that others had overlooked, and where current options were inadequate. During the 1990s, we tried repeatedly to develop a gene therapy treatment for cystic fibrosis. Even though we did not succeed, we learned a huge amount about gene therapy. Today, the company is applying this knowledge in its ongoing research with this technology, and I am convinced that our continued efforts will one day make a difference in patients' lives.

Despite the challenges, today is as exciting a time as any to be starting or running a biotech company. Over the last three decades, biotechnology has made incredible advances, and this is going to result in some remarkable breakthroughs for horrifying diseases such as Parkinson's and Alzheimer's in the decades ahead. To the young leaders in biotechnology, I say: don't give up. Stay focused. Don't believe people who say that you are crazy for trying something that no one has done before. Things will fail. But patients are counting on you to take what you've learned and try again.

Increased concentration

The big picture

Access is not equal

Biotechnology fund-raising has always been subject to (sometimes severe) fluctuations, with public-market windows opening and closing with some regularity. In the mid-2000s, however, we saw these fluctuations becoming less pronounced – a trend we attributed to public-market investors becoming increasingly specialized and savvy and demanding ever more data before making an investment. Companies with the right data and a sufficiently de-risked path to market had reasonably ready access to capital. But other companies – e.g., those at an earlier stage of development, with marginal data, or trying to rebound from a clinical setback – had far fewer options. The situation today is very similar, except that the end of the era of “easy money” has reduced the amount of capital available across the broader economy, and as a result, the remaining investors have set the financing bar higher. Investors are not just challenged by reduced liquidity; they are also compelled to assess regulatory and reimbursement risks (in addition to scientific risk) earlier in a product’s development cycle – a phenomenon that has discouraged “generalist” institutional investors from playing more heavily in the sector.

While the rebound in aggregate financing since the crisis has been impressive, the reality is that the funds are increasingly concentrated in a smaller cohort of companies – meaning that most companies are facing, and will continue to face, a rough financing road. In fact, 27% of the 2010 financing total was raised through debt offerings by mature public companies. The US\$16 billion available to pre-commercialization stage companies was actually a decrease from 2009 levels, despite a favorable environment in the

equity markets fueled by record low interest rates. The top 20% of US companies raised 83% of US funding in 2010.

As a result of this challenging environment, companies and their investors have had to realign their strategies. Many have restructured and focused their limited resources on a more narrow set of technologies. Others have chosen to partner with larger companies earlier, or on less generous terms, than they might otherwise have done. Those that could not make it had to cease operations. Despite the industry’s tremendous resilience, we can expect this thinning of the population to continue, at least until there is a significant change in the macro environment or in the incentives for investors to participate in the sector.

Metering the money

Venture capital fuels the early development of new innovation, and overall, investment levels stayed robust in 2010 as companies in the US, Europe and Canada raised US\$5.9 billion, a slight increase from the US\$5.8 billion raised in 2009. Behind these numbers, however, venture capitalists are challenged by significantly reduced capital flowing into their funds, are having to hold their investments longer before exiting, and are deploying capital differently. It has become increasingly common for investments, especially those in early-stage companies, to be doled out over time in several milestone-driven “tranches” (the charts in this report reflect publicly disclosed values, which almost invariably include all tranches). This financing strategy helps VCs manage total return on investment as they can pull capital from their investors in a more staged manner, but it also makes company managers increasingly focused on achieving near-term milestones to keep the money flowing.

Venture investors are insisting on more capital-efficient strategies from companies, with less fixed infrastructure and more outsourcing. They are strategically positioning their portfolios with both focused project-funding structures geared for early M&A exits and technology bets that are longer-term propositions. Pharma companies that are seeking access to new technologies are helping to partially fill the gap with increased corporate venture investing. As a result, biotech companies have seen a dramatic increase in financings that include multiple corporate venture investors.

IPOs for a select few

IPO investors who could once be counted on to take the funding baton from VCs and share in the development risk now require more proof-of-concept data and a more de-risked path to the market. While IPO proceeds from US and European listings crossed the US\$1 billion threshold for the first time since 2007, it is not surprising that the two largest US transactions of the year were done by a company with a drug in Phase III trials and a next-generation sequencing company that was already generating revenue. Similarly, the largest IPO in Europe (approximately one-fourth the size of the largest public launch in the US) was by a company with three compounds in Phase II development and multiple strategic alliances. Public investors remain selective and very price sensitive, as reflected by the fact that most offerings failed to price within their desired price ranges.

Capital raised in the US, Europe and Canada, 2000-10 (US\$m)

	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
IPOs	1,316	823	116	2,253	1,809	1,785	2,157	484	602	438	7,393
Follow-ons	3,454	6,579	1,840	3,345	6,303	4,600	3,398	4,046	1,070	2,431	15,675
Other	14,402	10,044	8,402	17,185	14,883	8,430	11,149	10,178	5,542	4,403	11,625
Venture	5,849	5,765	6,168	7,476	5,404	5,417	5,713	4,077	3,622	4,298	5,177
Total	25,021	23,211	16,527	30,258	28,399	20,232	22,417	18,785	10,836	11,571	39,870

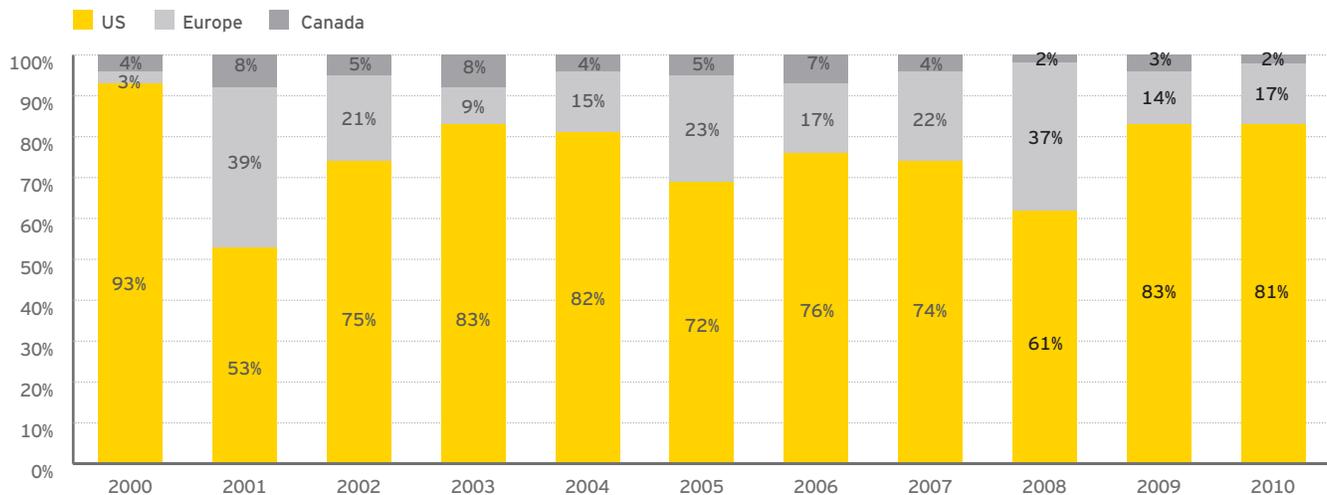
Source: Ernst & Young, BioCentury, BioWorld and VentureSource
Numbers may appear inconsistent because of rounding.

Companies in the US, Europe and Canada raised slightly more than US\$25 billion in 2010, an impressive 8% increase over 2009. This is roughly equal to the average amount raised during the four years immediately preceding the crisis – which is truly remarkable when one considers that two of those years, 2006 and 2007, saw sky-high financing totals during what now appears to have been a period of easy money. Venture funding was essentially flat compared to the year before, and IPO funding rebounded somewhat. The bulk of the growth in funding, however, came from the “Other” financing category, where mature, profitable

companies entered large debt transactions in a low-interest-rate environment.

However, as discussed later in this section, access to capital is not evenly distributed. Later-stage companies generally have ready access to funds, while earlier-stage public and private companies struggle to navigate the gap until their next development milestone. Europe and Canada remain particularly challenged, while both the debt and equity markets in the US have opened up on a selective basis.

Distribution of capital raised in the US, Europe and Canada by year

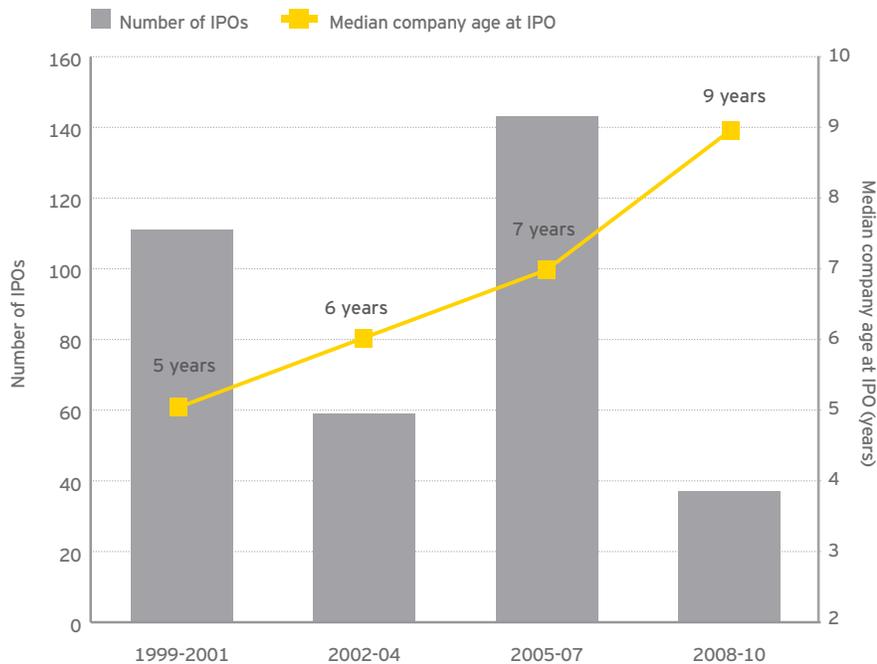


Source: Ernst & Young, BioCentury, BioWorld and VentureSource
Numbers may appear inconsistent because of rounding.

The US dominates global financings for biotechnology, and its share of funds raised has only increased since the onset of the economic crisis. The geographic distribution becomes slightly more balanced when debt raised by profitable companies is

removed from the picture. Measuring only capital raised by pre-commercialization biotechs, the 2010 shares change to 24% in Europe and 73% in the US.

An exit too far? The median age of IPO companies has increased steadily

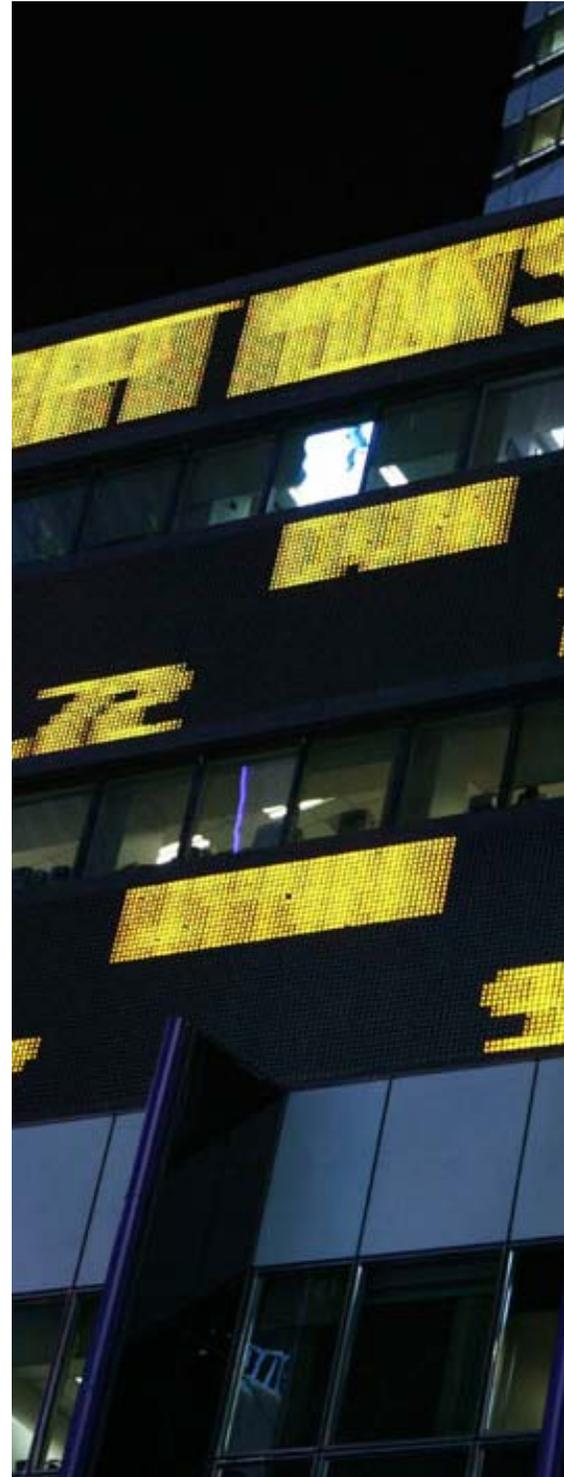


Source: Ernst & Young, BioCentury, BioWorld and VentureSource

The biotechnology industry has always needed – and, we would argue, continues to need – a healthy IPO market to flourish. While many companies and venture capitalists express a preference for an exit by trade sale, the number of active buyers isn't large enough for that to be a viable option for every company already in existence or being launched today. While the IPO market cracked open in 2010, with proceeds exceeding US\$1 billion, the reality of ever-longer periods to an IPO is placing increasing strain on the venture capital model. Return on investment is, of course, negatively impacted by longer holding periods. Equally challenging is the fact that most venture funds have 10-year lives by design. An average time to "liquidity" of nine years forces decisions on how to exit

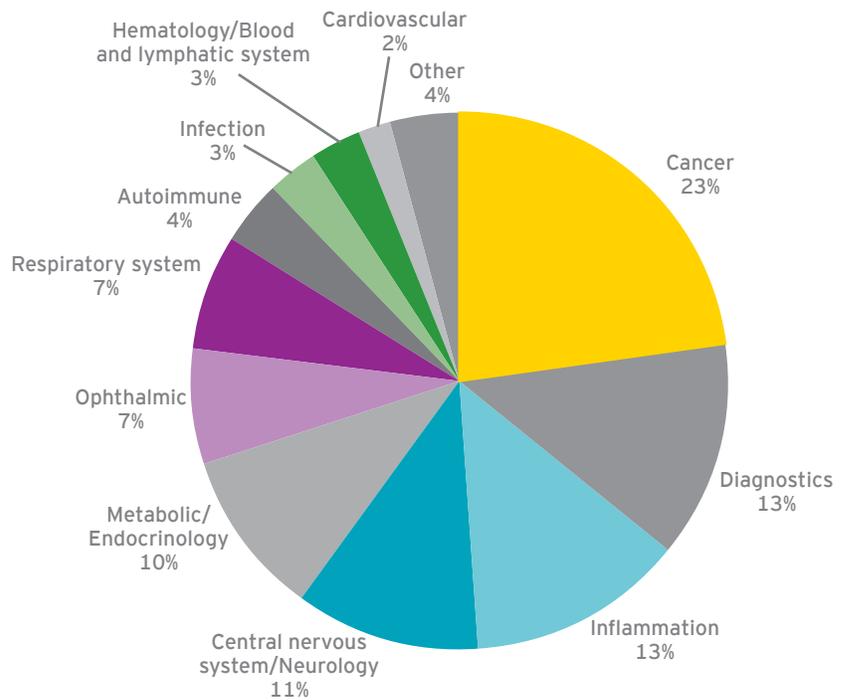
that may not be in the best interest of the company or its investors.

The reasons for this situation are varied: savvy public investors who want to see proof-of-concept data in hand; more complex scientific challenges being tackled; increasing regulatory demands; and in some cases, a reluctance to spend precious capital on the numerous regulatory requirements that come with being a public company. The reality of public investors demanding later-stage technologies is one of the primary reasons venture investors prefer to exit by trade sale when that option is available.





What are VCs funding? US and European seed and first-round financings over US\$5 million



Source: Ernst & Young, BioCentury, BioWorld and VentureSource
 Chart shows distribution of funds raised. For companies developing drugs with multiple indications, the amount raised was distributed equally across the different indications.

At a time when access to capital has become more challenging and VCs are having to hold their existing portfolio companies longer, it is worth examining where investors are placing their bets with regard to the next generation of start-ups. Not surprisingly, an analysis of seed and first-round venture investments reveals that companies with a cancer focus commanded the largest share of significant rounds (those over US\$5 million). Companies focused on diagnostics, inflammation and central nervous system ailments also attracted a healthy share of this funding. It is worth noting that very little of the money going to fund new companies went to

cardiovascular firms – a sign, perhaps, that investors are increasingly wary of a segment that is likely to face stiff competition from blockbuster products that are going off-patent and also require large and expensive clinical trials at a time of increased regulatory opacity.

United States

US yearly biotechnology financings (US\$m)

	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998
IPOs	1,097	697	6	1,238	944	626	1,618	448	456	208	4,997	685	260
Follow-ons	2,971	5,165	1,715	2,494	5,114	3,952	2,846	2,825	838	1,695	14,964	3,680	500
Other	12,242	7,617	6,832	12,195	10,953	6,788	8,964	8,306	5,242	3,635	9,987	2,969	787
Venture	4,409	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	20,720	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.

In the last two years, capital raised by the US industry has rebounded to pre-crisis levels. However, these numbers mask the issue of capital flowing to an ever more concentrated group of companies. The "Other" category above includes US\$3.7 billion and US\$9.4 billion in 2009 and 2010, respectively, of debt raised by profitable companies. These entities have taken advantage of historically low interest rates to raise funds principally to refinance existing debt and for stock buybacks and acquisitions. Excluding these financings, "innovation capital" raised by pre-commercial companies actually declined by 21% in 2010.

The US Government's Therapeutic Discovery Credit program, which received a great deal of press coverage during the year, added an additional US\$1 billion in 2010 funding. Unfortunately, because of the way the program was administered, each qualified program received just shy of US\$250,000. With more than 2,000 companies receiving some funding from the program, the impact on the companies tracked by this report was not significant.

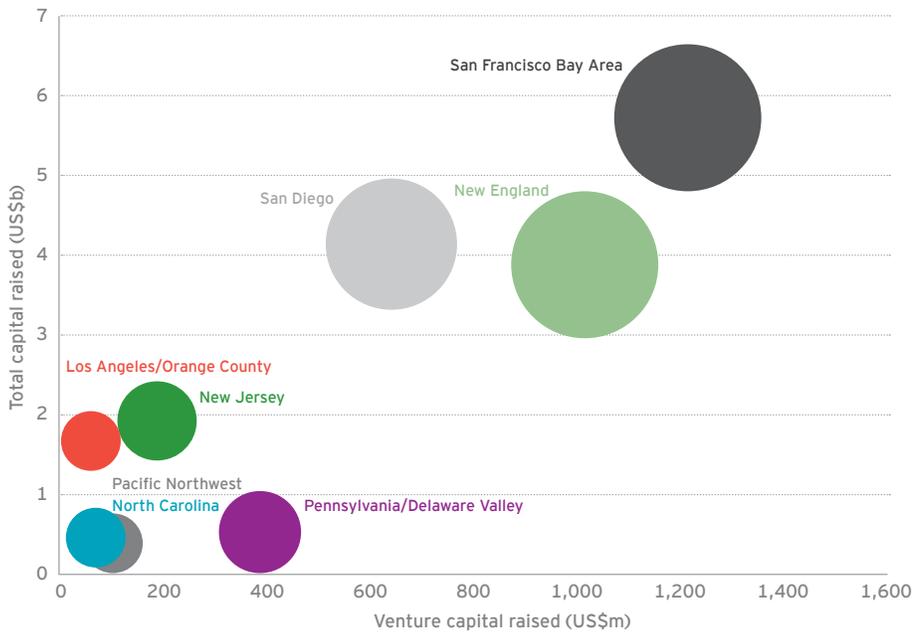
The positive trends in the second half of the year were due principally to the debt issuances by the profitable companies discussed above, with about US\$3.7 billion raised in the third quarter and US\$3.2 billion in the fourth quarter. Venture capital dropped greatly in the second half of the year, both in number of transactions and aggregate dollars raised, in part due to less capital available as firms struggled to raise new capital or strategically decided to raise smaller funds.

Quarterly breakdown of 2010 US biotechnology financings (US\$m)

	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	351 (4)	180 (3)	185 (3)	381 (5)	1,097 (15)
Follow-on	946 (20)	623 (17)	241 (5)	1,161 (22)	2,971 (64)
Other	1,017 (131)	1,514 (135)	1,123 (95)	755 (76)	4,409 (437)
Venture	2,016 (51)	2,152 (42)	4,508 (35)	3,565 (20)	12,242 (148)
Total	4,331 (206)	4,469 (197)	6,058 (138)	5,862 (123)	20,720 (664)

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 US regions, 2010

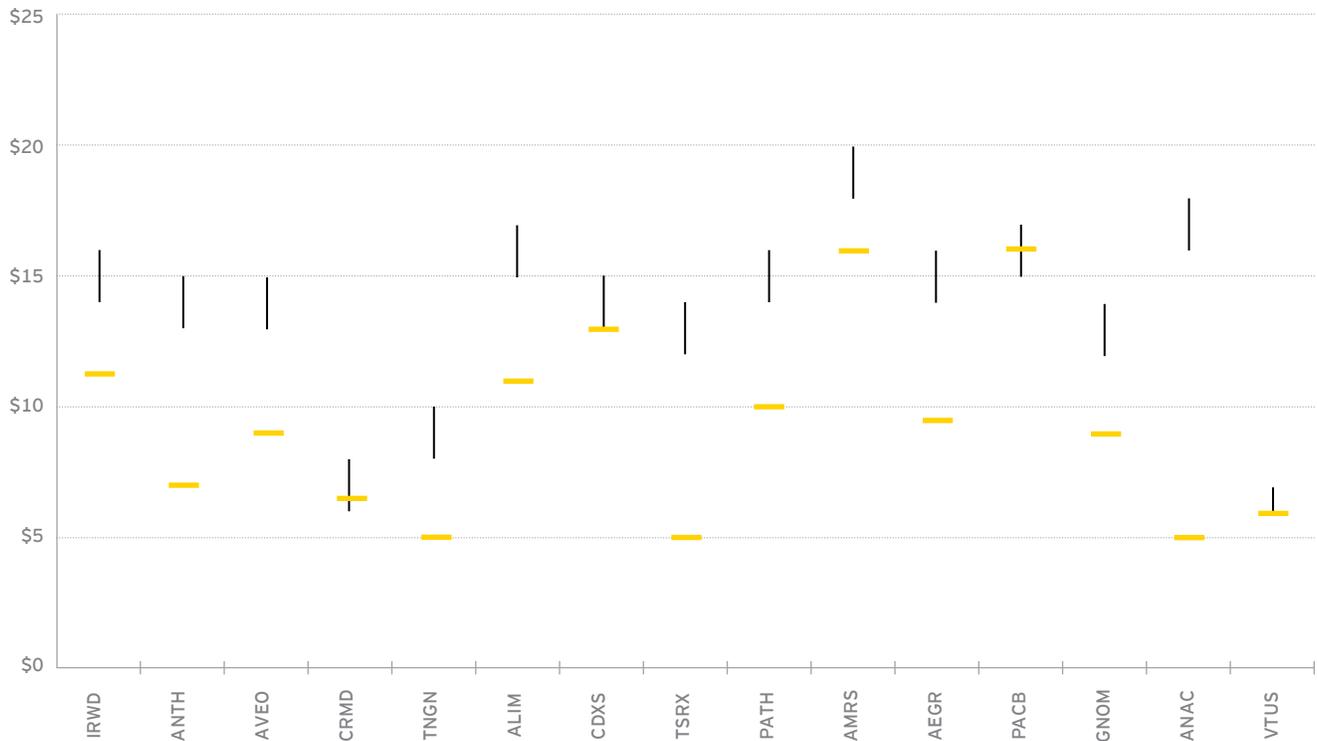


Source: Ernst & Young, BioCentury and VentureSource
 Size of bubbles shows number of financings per region.

The three largest clusters in the US continue to dominate the financing scene. San Diego edged ahead of New England in terms of total capital raised due to the US\$2.3 billion of debt raised by Life Technologies. The San Francisco Bay Area and New England continue to dominate venture capital financings, with each one raising in excess of US\$1 billion. Both clusters had considerable increases in total capital raised over prior years.



The vast majority of US IPOs priced below their desired ranges

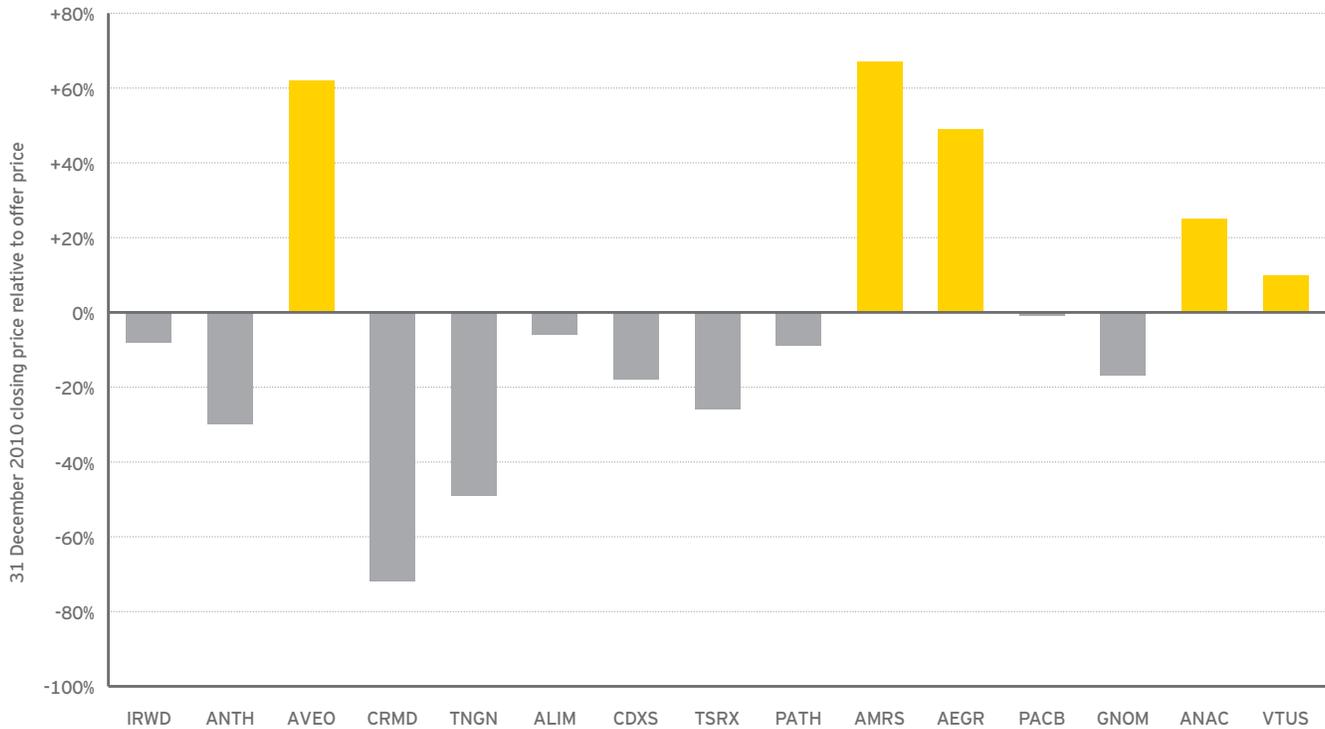


Source: Ernst & Young, finance.yahoo.com and media reports
 Vertical lines indicate IPO filing ranges; horizontal dashes indicate offer prices.

While the increased number of completed IPOs is a positive development in comparison with the prior two years, IPO investors were (and remain) price sensitive. Only two IPOs priced in the middle of their stated price ranges. Most deals had to take significantly less than planned in order to get the transaction done. Investors weren't just focused on the price; they were also focused on future dilution. In many cases, they requested that

companies issue more shares in the IPO at the lower price so that the total proceeds would be sufficient to fund operations until the next milestone. Existing investors played a greater role as well, frequently helping "fill the order book" by buying additional shares in the IPO transaction. The median market capitalization of the IPOs above was US\$160 million.

2010 US IPO performance



Source: Ernst & Young and finance.yahoo.com

Despite accepting a lower price per share in their IPO transactions, more than half of new issuers traded down between their debuts and the end of 2010. This trend reversed in 2011, with 10 of the 15 offerings trading in the red since their offering date as of press time. The 2011 IPOs that have taken place so far were also generally trading up, reflecting a run-up in overall US equity markets as a result of a low-interest-rate environment.

Europe

European yearly biotechnology financings (€m)

	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999
IPOs	165	103	75	737	682	803	365	32	144	211	2,482	162
Follow-ons	156	597	30	198	210	284	206	440	49	129	376	62
Other	1,540	1,390	938	3,552	2,601	1,125	1,645	1,287	178	684	1,494	155
Venture	1,021	790	1,031	1,210	1,511	1,428	1,520	924	1,332	1,695	2,012	639
Total	2,883	2,881	2,074	5,697	5,004	3,639	3,736	2,683	1,703	2,719	6,364	1,018

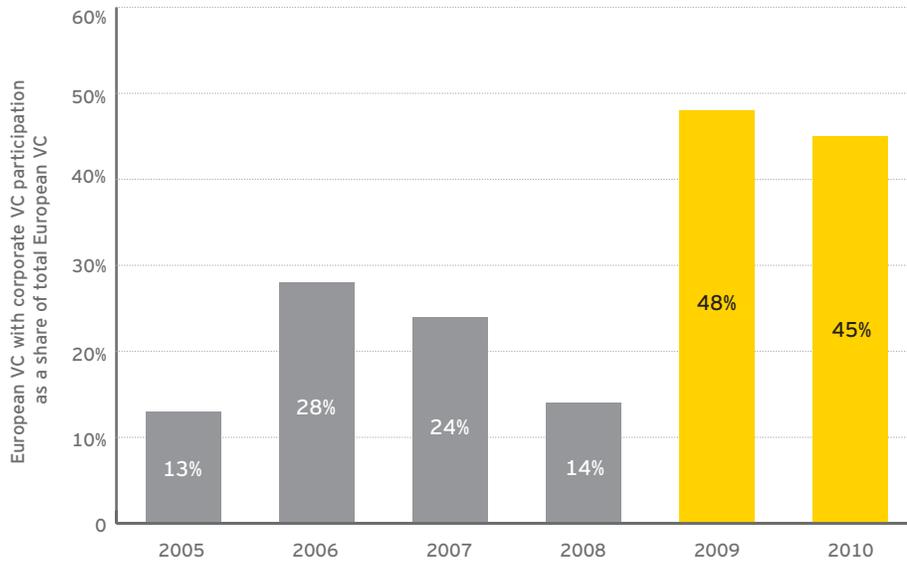
Source: Ernst & Young, BioCentury, BioWorld and VentureSource
Numbers may appear inconsistent because of rounding.

Capital raised by European biotech companies in 2010 was essentially unchanged from the prior year. However, looking behind the numbers, there are a couple of hopeful signs. The 2009 figures were dominated by two significant transactions that accounted for one-third of the total capital raised in the year, whereas in 2010, the funds were more equally distributed with no single transaction accounting for more than 6% of the total. In addition, venture capital recovered close to pre-crisis levels.

Unlike the US, which saw considerable amounts of debt raised by profitable companies, only Elan tapped the debt markets for a meaningful sum of money (US\$200 million) in Europe during 2010.



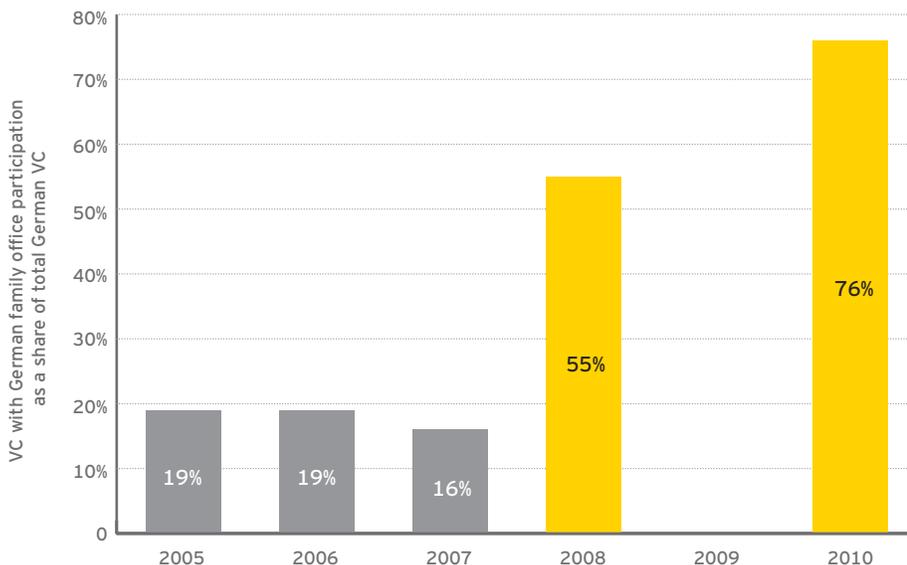
European corporate venture capital has increased since the financial crisis ...



Source: Ernst & Young, BioCentury, BioWorld and VentureSource

Even as the funding environment has become relatively more challenging in recent years, non-traditional sources of funding have become more prominent in funding European biotechnology companies. Corporate venture capital has come to account for a larger percentage of the total – funding raised through rounds with corporate venture participation accounted for 48% of European venture funding in 2009 and 45% in 2010 – up from an average of 20% in the four preceding years. (For more information on corporate venture funding, refer to *A closer look* on page 66.) Meanwhile, Germany's "family offices" – wealthy, family-controlled pools of capital – have become increasingly visible in that country's biotech scene.

... while Germany's family offices have become increasingly visible in the local market



Source: Ernst & Young, BioCentury, BioWorld and VentureSource

A closer look

Corporate venture capital in Europe



Siegfried Bialojan

Executive Director

Ernst & Young GmbH

Wirtschaftsprüfungsgesellschaft

While several large pharmaceutical companies have had corporate venture funds for some time, an increasing number of companies are now entering this space, including mid-sized pharmas. Most of these funds have historically been managed and measured based on financial returns, with a secondary focus on gaining exposure to potentially strategic technologies. More recently, as pharma companies revamp their business models to address the patent cliff and R&D productivity, corporate venture funds at many pharma companies have increased their activity and become more strategic about targeting relevant technologies, product ideas and process improvements.

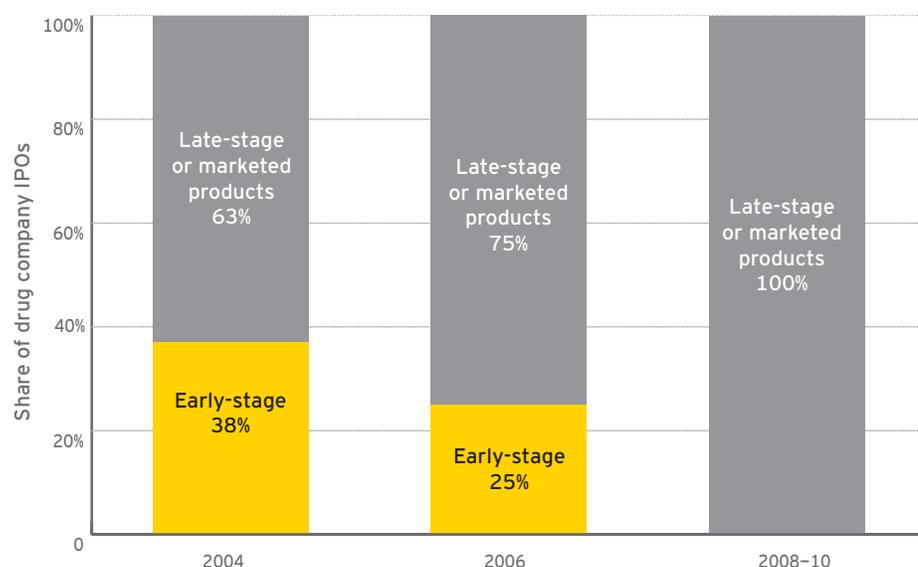
This step-up in activity has helped fill the void caused by consolidation in the traditional venture capital community, especially in Europe, where the number of active investors is decreasing, fund-raising has become extremely difficult and most financing has been restricted to existing portfolio companies in advanced stages of development.

Of the 10 largest venture-financing rounds in 2009, 9 included 1 or more corporate venture funds as a syndicate partner, with Novartis Venture Fund leading the field. This trend continued in 2010, with 12 of the top 20 venture rounds including a corporate

venture investor. Corporate venture funds are also investing in earlier financing rounds with particular emphasis on accessing and nurturing early technology developments that might be useful after proof of concept.

While traditional VCs once saw corporate venture participation as potentially limiting a biotech company's flexibility to partner with other pharmas, the reality is that corporate venture funding is now regarded as an important capital source. Corporate venture funds have to behave as pure financial investors in a financing syndicate; however, early access to information on new technology/drug development approaches is useful and can be strategically leveraged. VCs are even untroubled by situations in which the consortium has more than one corporate investor, since potential competition to in-license an asset can be resolved through an auction process in which even the loser (as a shareholder) might benefit from the competitor's success.

European drug company IPOs have shifted toward later-stage companies



Source: Ernst & Young, BioCentury, BioWorld and VentureSource

Numbers may appear inconsistent because of rounding. Chart excludes technology or service company IPOs. "Early-stage" shows preclinical or Phase I. "Late-stage" shows Phase II or III.

In another sign of investors imposing a higher bar on companies looking for capital, the pipeline maturity of companies going public in Europe has increased over time. In the IPO classes of 2004 and 2006, 38% and 25% of drug companies had early-stage products in development (pre-Phase II). Since 2008, however, all of the European drug company IPOs have involved firms with late-stage or marketed products.

Quarterly breakdown of 2010 European biotechnology financings (€m)

	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPO	27 (2)	57 (5)	22 (1)	58 (2)	165 (10)
Follow-on	114 (13)	13 (6)	6 (4)	23 (3)	156 (26)
Venture	273 (61)	308 (54)	275 (31)	165 (35)	1,021 (181)
Other	441 (41)	359 (34)	230 (24)	511 (42)	1,540 (141)
Total	856 (117)	737 (99)	533 (60)	757 (82)	2,883 (358)

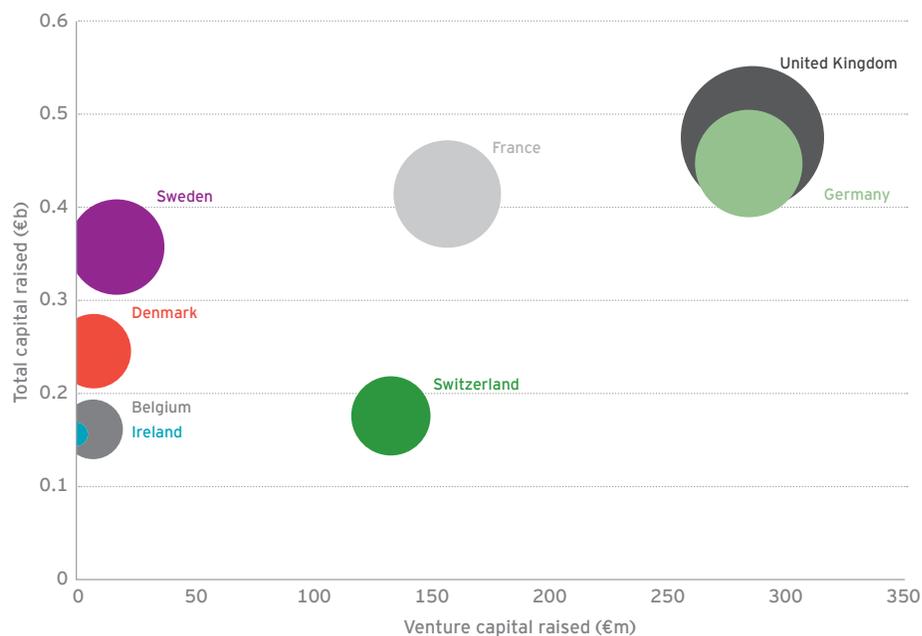
Source: Ernst & Young, BioCentury, BioWorld, Windhover and VentureSource

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

There was slightly less capital raised in the second half of the year. However, this was influenced more by the timing of certain significant transactions than to a change in market environment or investor sentiment. On the whole, investors remained cautious and selective toward the sector.

The UK has traditionally raised more capital than any other country in Europe. While that did not change in 2010, it is noteworthy that nearly 60% of capital raised by UK-based companies was in the form of venture capital – a considerably larger share than in prior years. Venture investing also dominated the scene in Germany, which rebounded strongly from a very low total in 2009. France's total was boosted by the €152 million raised by Transgene – a transaction that represented approximately one-third of the total raised in that country.

Capital raised by leading European countries, 2010



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

Canada

Canadian yearly biotechnology financings (US\$m)

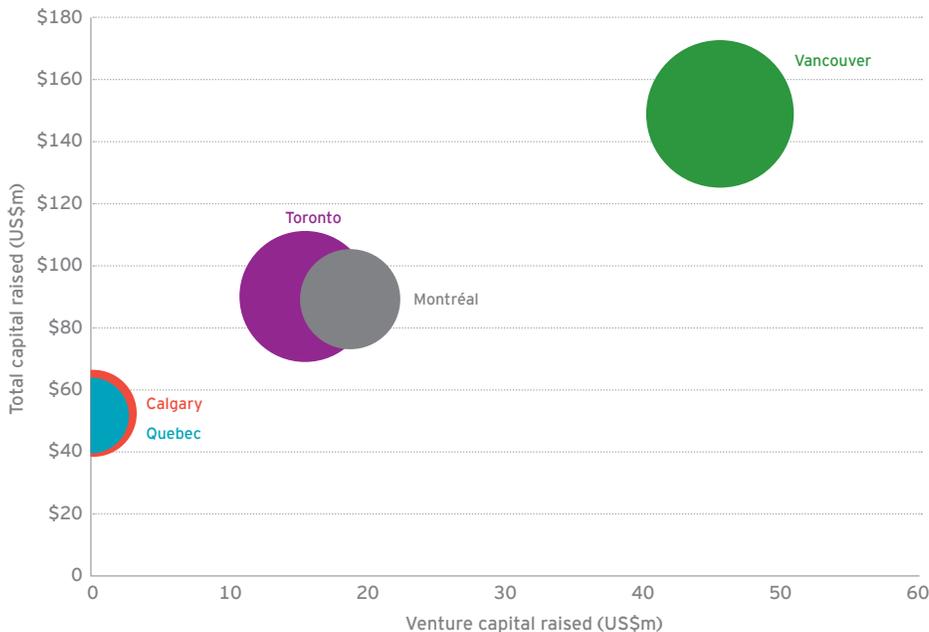
	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
IPOs	0	0	0	5	9	160	85	0	10	42	103
Follow-ons	276	138	80	580	925	295	296	723	186	621	364
Other	120	495	191	122	664	242	139	416	132	155	258
Venture	87	100	207	353	205	313	271	206	199	388	546
Total	482	733	478	1,060	1,803	1,010	791	1,345	527	1,206	1,271

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

In 2010, the Canadian biotechnology industry raised slightly more than US\$482 million, a decrease of US\$251 million compared to 2009. However, if we remove the US\$325 million raised by Biovail in 2009, the sector actually raised 18% more in financings compared to 2009. Public companies (excluding

Biovail) raised US\$396 million, a US\$88 million increase over 2009. Although Canada saw an overall increase in total financings in 2010, the amounts raised are still the second-lowest since 2000, with the majority of funds flowing to only a small number of companies.

Capital raised by leading Canadian biotech clusters, 2010



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

The relative position of leading clusters changed in 2010, with Vancouver leading the pack in both total financings and venture capital financings and surpassing traditional leaders Toronto and Montréal.

On a quarterly basis, the amounts raised were relatively consistent throughout the year. Conversely, during 2009, almost 75% of the deals occurred during the second and third quarters. The good news is that, based on a preliminary review of the first quarter of 2011, the slight upward trend observed in the fourth quarter of 2010 appears to be continuing.

Quarterly breakdown of 2010 Canadian biotechnology financings (US\$m)

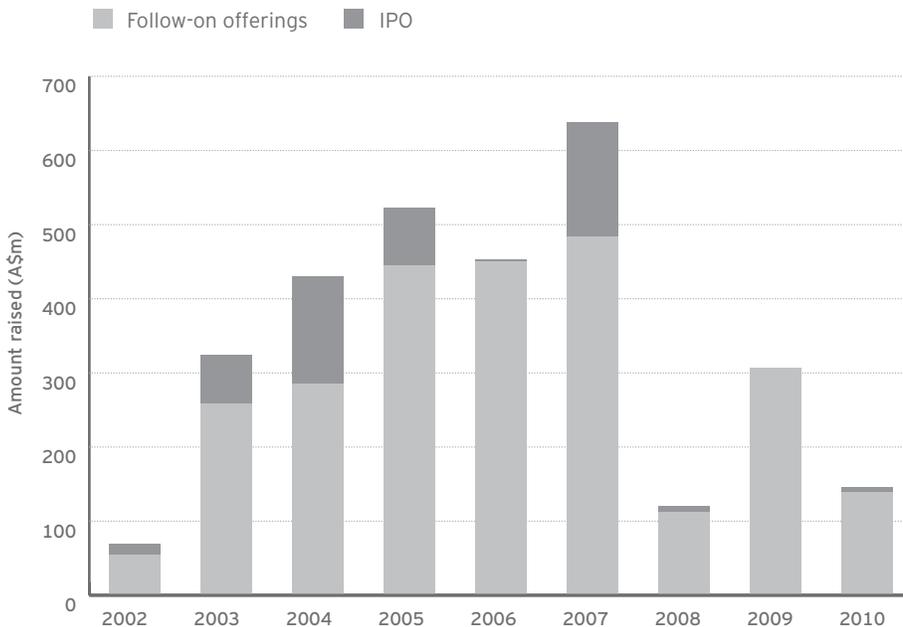
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Follow-on	99 (9)	44 (9)	23 (4)	111 (11)	276 (33)
Venture	6 (4)	46 (4)	28 (3)	7 (4)	87 (15)
Other	19 (8)	26 (2)	56 (7)	19 (7)	120 (24)
Total	124 (21)	115 (15)	106 (14)	137 (22)	482 (72)

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



Australia

Australian biotech public equity raised, 2002-10



Source: Ernst & Young, Bioshares and company annual reports

The funding situation in Australia, which took a turn for the worse after the global economic downturn, has yet to return to pre-crisis levels. Australian public biotech companies raised A\$146 million (US\$129 million) in 2010 – less than half the amount raised in 2009. While investors are certainly investing in the health care sector, relatively less seems to be going to biotech; instead, money appears to be primarily headed to medtech companies, which raised approximately A\$400 million (US\$354 million) during the year, including A\$85 million in a single IPO (Reva Medical).

The biotech IPO market remained weak throughout the year. One IPO did get off the ground in the first quarter, when Brisbane-based CBio raised A\$7 million (US\$6 million). However, no other Australian companies were able to go public during the rest of the year, indicating that the IPO window has not really opened up. In January 2011, Canada-based Bioniche listed on the Australian Stock Exchange, and there is now renewed hope that more companies will go public in 2011. ►

Project financing: from strategy to implementation



Axel Polack, MD
TVM Capital
General Partner, Life
Science Venture Team

“Biotech’s last rite” – a recent headline in the British magazine *Real Deals* suggests that the biotechnology industry’s venture model is dead. Indeed, people in research, drug development, politics, pharma and the financial community are feverishly experimenting with new models promising increased capital efficiency, shorter development cycles and higher-quality output. At TVM Capital, we are focused on creating companies around clearly defined single drug development projects. We aim to take these projects to proof of concept in a quick, lean and cost-efficient manner for sale or out-licensing to pharma companies, which are clearly hungry for such assets. However, the implementation of such a business model requires radically different approaches and competencies by both venture investors and management.

Successful implementation

Venture funding has always been based on three key elements – deal sourcing, monitoring and exiting – and successfully implementing a project-funding strategy will require new approaches and skills in each of these elements. Our *deal sourcing* occurs from two suppliers: academic research and pharma/biotech industry R&D. We see no shortage in the supply of potential projects. Pharma is willing to contribute programs without many strings attached, while universities are increasingly pushing projects further to the “preclinical candidate” stage with grant or governmental seed funding

instead of trying to spin them out at the screening stage.

Monitoring these deals requires a very different approach to running operations, managing risk and identifying go/no-go criteria. Since we are not building fully integrated companies, asset development is run by a small team with management expertise and specific technical know-how. This team is substantially supported by handpicked external advisers – who may also support other projects, depending on commonalities in phase of development and required expertise. It is essential that the actual project operations (pharmacology, toxicology, CMC clinical testing, etc.) are carried out by certified contract research organizations (CROs). This allows the academic inventor to continue to lead and advise the project, with the assistance of an externalized research department. Scientists, management and external advisers are motivated to maximize efficiency by a substantial share at exit. At the same time, clear criteria have to be defined to stop a project and limit potential losses.

Investment management changes in significant ways. With a lower burn rate, companies do not need further creative financing strategies such as partnering, and follow-on financing becomes less important. While the human resources needs of projects are less than those of full-fledged companies, substantial numbers of jobs will be created in related service areas such as CROs. VCs are more closely involved in running projects. This means they need to ensure that efficient matrix management is installed between the project team, external advisers and CROs. At the same time, portfolio management becomes more complex, since scientific risk will need to be diversified in VC portfolios, rather than

in the pipelines of individual companies. This puts increased demands on VC teams with respect to providing complementary professional expertise to the projects they fund.

As mentioned earlier, our *exiting* objective is the sale or out-licensing of a focused drug discovery project to the innovation-thirsty pharmaceutical industry after successful proof of concept. Ideally, the allocation of proceeds is transparent to all shareholders from the beginning of the project. Since a project typically needs less than US\$20 million, there should ideally be no need for follow-on financings and further dilution.

Summary

The interests of four groups (originators, management, VCs and CROs) can be balanced much more efficiently and effectively with a project-focused approach. VCs can achieve better returns through earlier exits and can – as a side effect – act as important strategic partners to the pharmaceutical industry. More than ever, VCs will function as gatekeepers to biotech innovation, provided they can demonstrate the necessary professional and scientific expertise. With our track record in the traditional biotech VC model and the experience we have already gained in funding project-focused companies such as Albireo and Proteon, TVM Capital Life Science Ventures is excited to be at the forefront of developing new approaches for funding biotech innovation. ►

Addressing risk: options and earn-outs

The big picture

Where are the acquisitions?

Biotech investors large and small – from venture capitalists to activist public investors – are increasingly focused on mergers and acquisitions as the best way to realize value from their holdings. As VCs are having to nurture portfolio companies for ever-longer periods before taking them public – and are seeing relatively low public market valuations when they do – many of them have concluded that an exit via a trade sale is the only sensible path. Indeed, many VCs now have a portion of their portfolios invested in low-burn-rate “build-to-sell” entities – essentially research projects. These investors are also wary of collaborations that might encumber too much of a company’s assets and reduce the number of potential acquirers. Meanwhile, activist investors in the US and Europe have consistently expressed the view that profitable biotechs can maximize shareholder value (in the short-run, at least) by selling to revenue-hungry pharma companies rather than by pursuing high-risk R&D. Public investors are increasingly looking for opportunities to capture some of the expected deal premium by investing in likely acquisition targets (ironically, this can be self-defeating by sometimes driving the value of the company beyond the reach of most acquirers). Pharma companies are virtually united in their view that they have to complement their internal R&D efforts by aggressively looking externally for breakthrough innovations and products, albeit with a preference for utilizing creative risk-sharing structures whenever possible.

All signs, it would appear, point to increased acquisition activity. So why are biotech M&A transaction volumes and values not increasing at an accelerating rate? There is

a variety of factors at work. Given a choice, a pharma acquirer will normally opt for an alliance over an outright acquisition in order to mitigate risk. The recent wave of megamergers has reduced the pool of potential acquirers, and has further distracted several would-be buyers by focusing their attention on post-merger integration issues. Further, many of these companies are facing a variety of challenging capital allocation decisions, including: whether to pursue acquisitions in other areas (e.g., to gain access to emerging markets); how best to reprioritize internal R&D portfolios; and the best means to provide shareholders the returns they seek through dividends and stock buybacks in a period of very low price-earnings ratios.

Thus, while we will continue to see headline-grabbing acquisitions of companies that have just launched their first drug (provided they don’t rapidly become too expensive) and the occasional megadeal, we are unlikely to see a significant increase in pre-commercial deal-making in the near term. Pharma buyers will continue to be selective, looking for the right mix of therapeutic fit, risk-mitigating structures (options and earn-outs) and price. There is a window of opportunity for big biotechs to play the consolidator role and diversify their own portfolios, but they, too, have seen price-earnings compression and have responded in part with stock buybacks of their own.

Sharing the risk

Just as investors are grappling with not just technology risk but also regulatory and reimbursement risk, so are potential acquirers/licensees. This trend, combined with the fact that a tight capital market has created a buyer’s market, has led to a variety of risk-sharing structures. Unless there is a strong desire to lock up



a particular technology, acquirers would typically opt for a strategic alliance over an acquisition since this limits their cost and risk to the particular program. While alliance activity remained strong in 2010, the average up-front license fee fell significantly relative to prior years, which is indicative of the desire of buyers and licensees to share development risk with their partners and “pay for performance” through milestones.

Acquisitions of venture-backed companies will continue to frequently include another form of milestone, contingent value rights (CVRs), under which a significant portion of the purchase price will be paid only upon the achievement of predefined milestones. These transactions are palatable to venture investors if the up-front payment represents a reasonable return and the earn-out period for CVRs (which represent additional potential upside) doesn’t extend too far beyond the life of the venture fund. While CVRs have been used in public-company acquisitions in the past, Celgene’s 2010 acquisition of Abraxis was the first deal in which the CVR was in the form of a security that trades publicly. This structure was also adopted by Sanofi in its 2011 acquisition of Genzyme. (For more on this structure, refer to *A closer look* on page 77.)

In another variant of risk-sharing, option-based deals remained very visible in 2010. In such transactions, pharma or big biotech companies pay for the option to acquire

a program or company after a specified milestone. The option payment can stay in the company to help fund development and/or be distributed to shareholders as a partial return on investment. As noted above, and further explored in the article by Axel Polack of TVM Capital (see page 72), many venture capitalists are following a strategy of establishing and funding low-infrastructure, capital-efficient “virtual” companies. These companies typically have a limited research focus, generally around a single asset, and are designed to be sold once key milestones are achieved. In some instances, investors chart a path to exit by identifying a potential buyer at inception (the buyer may even be the source of the technology under development). In a creative twist on this idea, Boston-based Third Rock Ventures formed a company, Ablexis LLC, around an antibody technology that it expects to license broadly. Since acquisition by one party is not the likely exit,

the company has a tax-efficient structure under which ongoing license payments received can be continuously distributed to shareholders.

Medtech as a model?

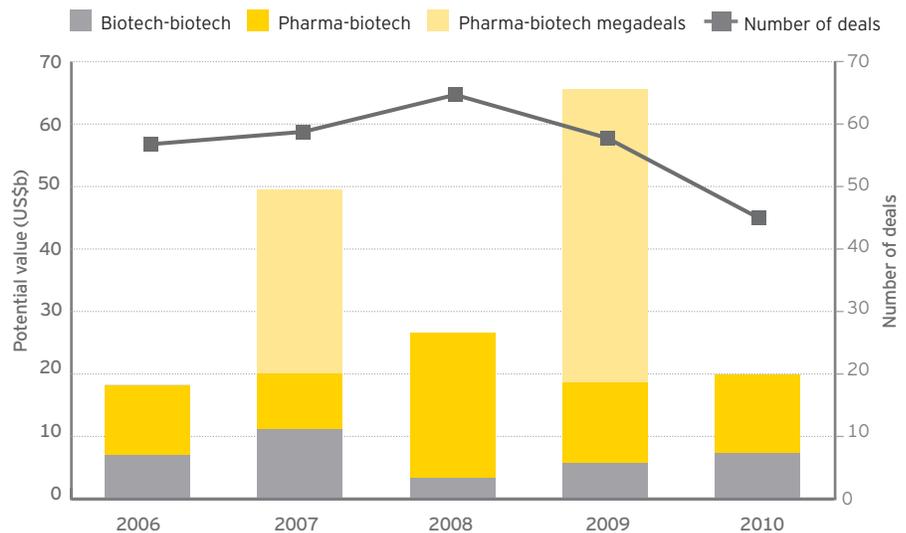
Some have speculated that the “build-to-sell” company approach is moving biotech toward the longtime model of the medtech industry, in which companies are formed around technologies that fit a market need and slot easily into the product portfolios of an identified group of potential acquirers. Under this model, very few companies ever attempt an IPO. While the parallels exist, it is unlikely that this will become the predominant model for biotech because of the extended R&D time frames for breakthrough therapies and the more rigorous product approval process for drugs.

Increasing hostility?

Despite the interest investors have in reaping a return through a trade sale, a surprising number of deals in the recent past have started as hostile transactions, including Astellas Pharma’s acquisition of OSI Pharmaceuticals, Sanofi’s takeover of Genzyme and the recent overtures by Valeant Pharmaceuticals to Cephalon (before the latter settled on Teva Pharmaceuticals as a suitor at a significantly higher valuation; for more on Cephalon’s approach to deals, see the interview with Kevin Buchi on page 84). The conventional wisdom has been that hostile takeovers don’t work well in an industry in which the target’s scientists are among its most valuable assets. It appears that suitors in certain situations are willing to take the risk of offending and losing the target’s employees in an effort to secure the deal.

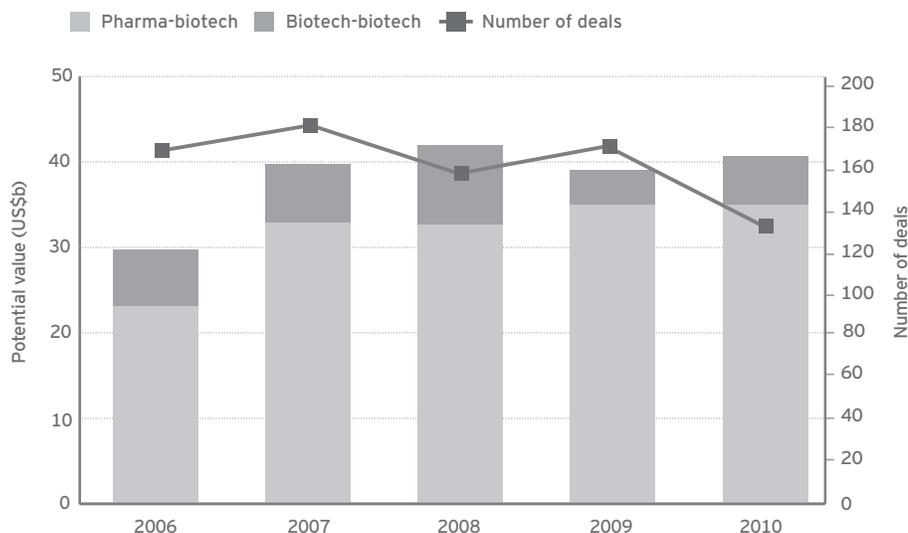
Any expectations of a pickup in M&A activity due to the financing challenges of biotech companies and the pipeline needs of pharma acquirers were unfulfilled in 2010. The volume of M&A transactions involving US or European biotech firms was down sharply, while the aggregate values of these transactions were relatively flat (after excluding the skewing effect of megamergers larger than US\$10 billion from the totals).

US and European M&As, 2006-10



Source: Ernst & Young, Windhover Information, MedTRACK and company websites
 Chart excludes transactions where deal terms were not publicly disclosed. The 2010 totals also exclude Sanofi/Genzyme, because the parties did not agree on terms until 2011, and Grifols/Talecris, because the transaction was subject to continuing antitrust review risk in 2010.

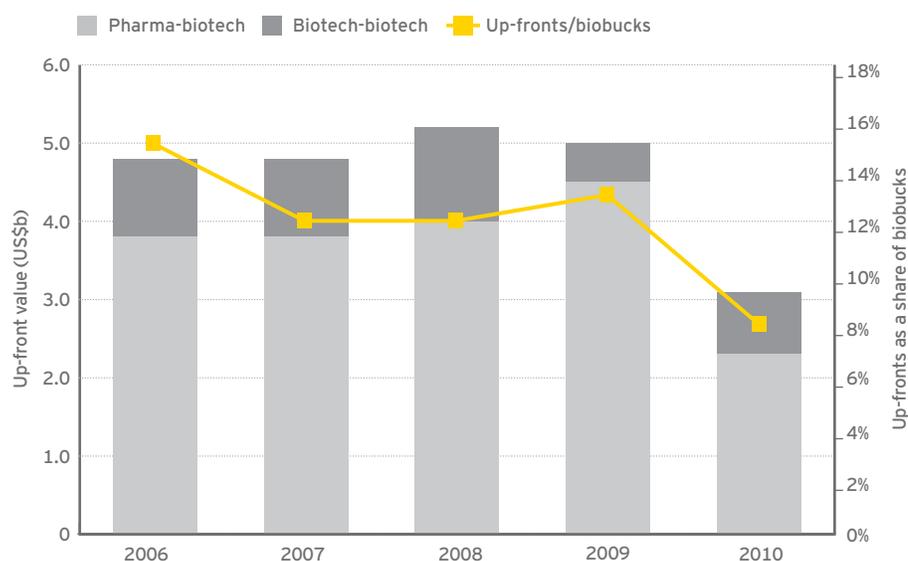
US and European strategic alliances remain strong based on biobucks ...



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

It has long been a common practice for companies to trumpet the total *potential* value of alliances in their press releases – so much so that the industry has its own term for these measures: “biobucks.” While it has always been clear that these total amounts are almost guaranteed never to change hands (since doing so would require the statistically implausible achievement of every milestone), biobuck amounts have been accepted as an indicator of buyer sentiment and the value that pharmaceutical companies are ascribing to biotech assets.

... while up-front payments declined sharply



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

But there is now a widening gap between the high total values being announced and the cash actually flowing in to fund biotech innovation. Licensees have become more risk-conscious, with up-front license fees and other payments declining sharply, especially for earlier-stage technologies. This trend also reflects a challenging financing environment – many companies know they must partner, in some cases earlier in the development cycle than desired, giving buyers more leverage.

There was no “defining” deal in 2010, as big pharmas largely stayed on the sidelines despite the need to acquire revenue-generating products to help them plug the gap created by patent expirations. (Sanofi’s pursuit of Genzyme through much of 2010 did not close until early 2011 and is excluded from these numbers.) That transaction as well as the second-largest deal of 2010 – Celgene’s acquisition of Abraxis – utilized contingent value right securities that trade in the public market. It is noteworthy that every acquisition of a venture-backed company in the accompanying table also included CVRs. (For more detail on CVRs, refer to *A closer look* on page 77).

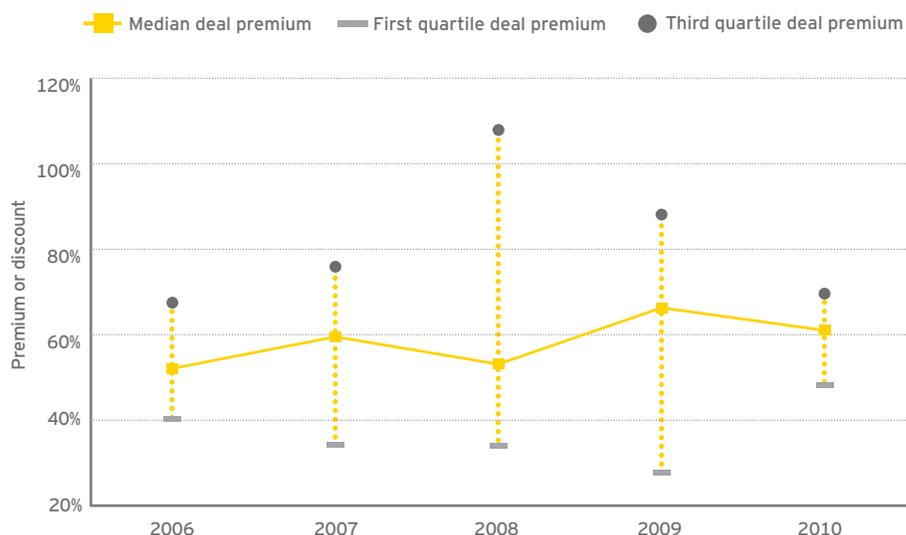
Selected M&As, 2010

Company	Country	Acquired or merged company	Country	Value (US\$m)	CVRs/ milestones (US\$m)
Astellas Pharma	Japan	OSI Pharmaceuticals	US	4,000	-
Celgene	US	Abraxis BioScience	US	3,550	650
Biovail	Canada	Valeant	US	3,200	-
Johnson & Johnson	US	Crucell	Netherlands	2,318	-
Bristol-Myers Squibb	US	ZymoGenetics	US	885	-
Life Technologies	US	Ion Torrent Systems	US	725	350
Abbott Laboratories	US	Facet Biotech	US	722	-
Cephalon	US	Mepha Pharma	Switzerland	590	-
Axcan Pharma	Canada	Eurand	Netherlands	583	-
Shire	UK	Movetis	Belgium	567	-
Sanofi	France	TargeGen	US	560	-
Merck & Co.	US	SmartCells	US	500	-

Source: Ernst & Young, Windhover Information, MedTRACK and company websites

As volatility has come down since the financial crisis, the range of deal premiums paid in acquisitions of public companies has narrowed to the tightest band seen in the last five years. The median premium in 2010 was approximately 60%.

Deal premiums in acquisitions of public companies



Source: Ernst & Young and Capital IQ
Deal premiums show premium or discount relative to average price during the month prior to announcement.

A closer look

CVRs close the gap



Jeffrey Greene
Partner
Ernst & Young LLP

M&A structures that include some form of contingent consideration – based on future sales, profits or event-driven milestones – have been a popular means of bridging valuation gaps and sharing risk between buyers and sellers for some time. These structures have been employed with increasing frequency in recent years in acquisitions of private biotech companies, which, by definition, are controlled by a limited number of shareholders. These shareholders – typically venture capitalists – have sought a reasonable “up-front” exit that provides a modest return on investment, with the prospect of a much bigger return later if the contingencies are resolved favorably.

The earn-out or milestone structure has also been used in the acquisition of small-cap public companies, such as The Medicines Company’s acquisition of Targanta Therapeutics in 2009 and the 2010 acquisition of Trubion by Emergent BioSolutions. In such situations, the target companies, while publicly traded, have also had fairly concentrated groups of shareholders. In 2010 and early 2011, the use of contingent structures reached a new level of sophistication, first in Celgene’s acquisition of Abraxis, and then most notably in Sanofi’s takeover of Genzyme. The latter transaction started out as a hostile tender, but it turned friendly after a period of negotiation during which the contingent consideration was critical in bridging the valuation gap between the buyer and sellers. But in these two transactions – unlike the acquisition of private companies – the milestone rights are embodied in a publicly traded security, a contingent value right (CVR).

CVRs are initially recorded as a liability and are “marked to market,” using either publicly quoted prices (if the CVR is actively traded) or other means of estimating fair value, and any adjustments are reflected as a component of operating earnings. Fluctuations in the value of the CVR can therefore contribute to earnings volatility during the contingency period. The buyers in these transactions typically are required to perform some level of diligence in pursuing the milestones and must ensure that internal systems are robust enough to track the relevant performance data.

Of course, the tax consequences of a CVR structure vary by jurisdiction. If the buyer acquires shares of the target, the CVR creates additional tax basis in the stock when the amount becomes fixed and payable and may create tax deductions at that time if a portion of the CVR is paid out to former option holders. If the transaction was structured as an asset acquisition, the CVR will generally create more amortizable intangible assets when the amount becomes fixed and payable. A seller that receives a publicly traded CVR as consideration would generally include the value in the determination of any taxable gain. A seller receiving a nontransferable CVR will be treated as having sold the shares in an installment sale transaction and can generally defer a portion of the gain until the contingent consideration is recognized.

The number of announced deals with potential values greater than US\$1 billion increased from 9 in 2009 to 12 in 2010. It is noteworthy that the buyers included three Japanese companies but no US-headquartered big pharma. In fact, no US big pharma was represented in the top 20 transactions based on announced potential deal values. Meanwhile, GlaxoSmithKline and AstraZeneca continued to remain active in forming large alliances – both companies had alliances with potential values greater than US\$1 billion in 2009 as well as 2010.

Big biobucks alliances, 2010

Company	Country	Partner	Country	Total potential value (US\$m)	Up-front payments (US\$m)
Boehringer Ingelheim	Germany	MacroGenics	US	2,160	60
Cephalon	US	Mesoblast	Australia	2,050	350
Bayer Schering Pharma	Germany	OncoMed Pharmaceuticals	US	1,937	40
Boehringer Ingelheim	Germany	f-star	Austria	1,700	Undisclosed
GlaxoSmithKline	UK	ISIS Pharmaceuticals	US	1,500	35
Eisai	Japan	Arena Pharmaceuticals	US	1,370	50
Kyowa Hakko Kirin	Japan	Dicerna Pharmaceuticals	US	1,324	4
AstraZeneca	UK	Rigel Pharmaceuticals	US	1,245	100
Roche	Switzerland	Aileron Therapeutics	US	1,125	25
Forest Laboratories	US	TransTech Pharma	US	1,105	50
GSK	UK	Proteologics	Israel	1,070	3
Takeda Pharmaceutical	Japan	Orexigen Therapeutics	US	1,050	50

Source: Ernst & Young, Windhover Information, MedTRACK and company websites
 "Total potential value" includes up-front, milestone and other payments from publicly available sources.

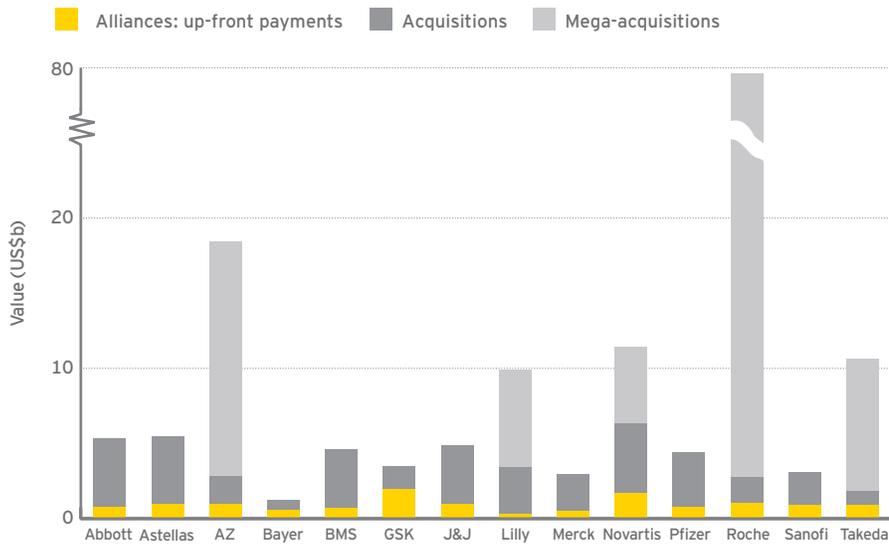
A more relevant measure of value is the up-front payments that actually change hands upon signing – typically as license fees or the sale of equity. While Abbott's transaction with Reata grabbed headlines as the largest up-front ever, the number of deals with up-front payments greater than US\$75 million declined by half, from 16 in 2009 to only 8 in 2010.

Alliances with big up-front payments, 2010

Company	Country	Partner	Country	Up-front payments (US\$m)
Abbott Laboratories	US	Reata Pharmaceuticals	US	450
Cephalon	US	Mesoblast	Australia	350
AstraZeneca	UK	Rigel Pharmaceuticals	US	100
Ipsen	France	Inspiration Biopharmaceuticals	US	85
Biogen Idec	US	Knopp Neurosciences	US	80
Meda	Sweden	Norgine International	UK	75
Abbott Laboratories	US	Neurocrine Biosciences	US	75
Astellas Pharma	Japan	Basilea Pharmaceutica	Switzerland	72

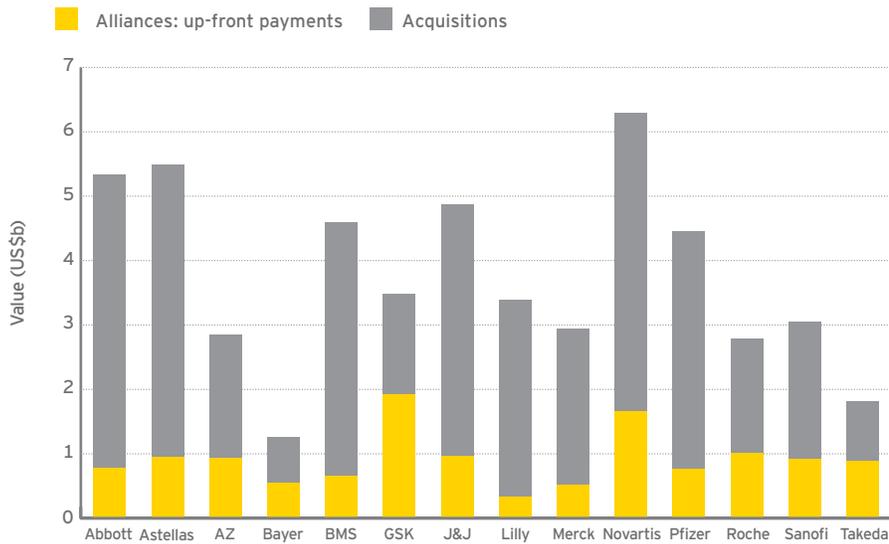
Source: Ernst & Young, Windhover Information, MedTRACK and company websites

Strategic buyers: biotech acquisitions and alliances by big pharma companies, 2005-10



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

Biotech acquisitions and alliances by big pharma companies (excluding mega-acquisitions), 2005-10



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

While partnering with and acquiring biotech companies are important components of the strategy of all pharma companies, there are some differences in activity levels across firms. To obtain a more stable picture of activity, we conducted our analysis over the last six years. And since mega-acquisitions can distort the overall picture, we looked at the totals with and without these megadeals. Lastly, we only included up-front values of strategic alliances, since it is highly uncertain that the total biobucks amount will ever change hands.

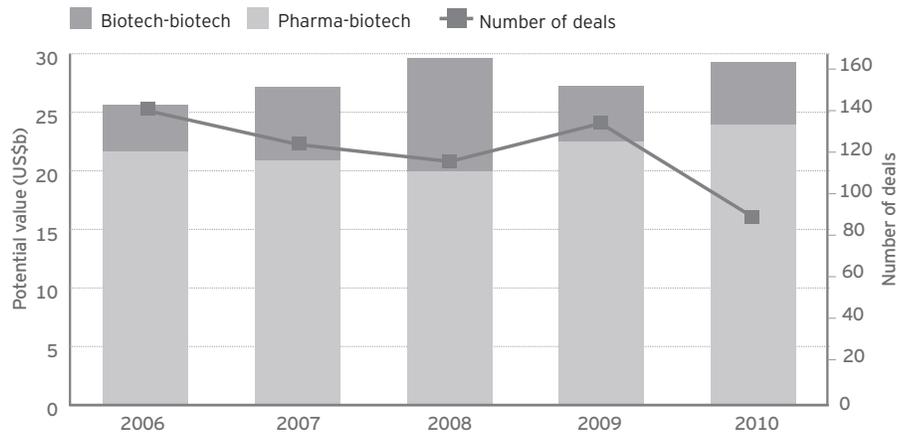
Novartis and its crosstown rival, Roche, stand out. Novartis is the largest deal-maker when megadeals are removed (and is third even when megadeals are included). The company also places second in terms of strategic alliance up-front payments. Meanwhile, Roche is at the top of the heap overall, thanks to its mega-acquisition of Genentech. Japanese pharma companies, which have historically not been very active buyers overseas, have become increasingly visible in recent years. Astellas, in particular, ranks second in the biobucks-adjusted totals, while Takeda ranks fourth in the overall totals. (In another sign of the increasing activity by Japanese pharma companies, Takeda announced that it was acquiring Nycomed as this report headed to press.)

United States

Announced deal values involving US companies remain strong with pharma-biotech deals increasing for the third consecutive year.

Up-front payments in alliances have declined significantly year over year, both in the aggregate and as a percentage of potential deal values, reflecting increased risk-sharing among the parties and the continuation of a buyers' market for products.

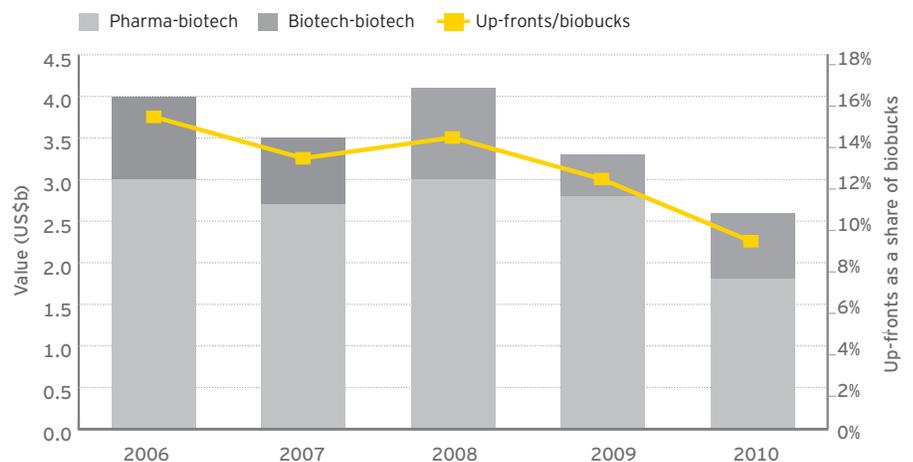
US strategic alliances remain strong based on biobucks ...



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

Chart shows potential value, including up-front and milestone payments, for alliances where deal terms are publicly disclosed.

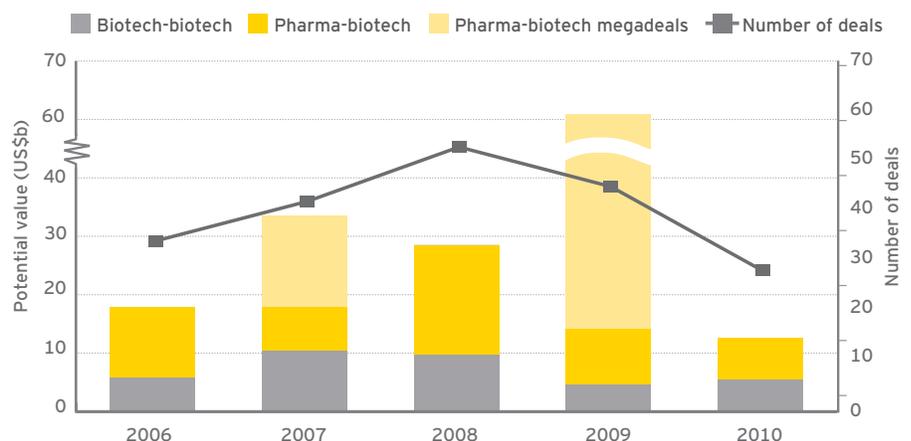
... while up-front payments declined sharply



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

M&A transactions involving US biotech companies turned in the lowest aggregate value in the last five years – a surprising result given the number of companies that see M&A as their exit strategy. The 2010 totals continue a downward trend in total deal values (after adjusting for Roche's 2009 acquisition of the minority interest in Genentech) that began at the time of the financial crisis. This trend reversed somewhat in early 2011, with Sanofi's mega-acquisition of Genzyme and high-profile private deals such as Daiichi Sankyo's acquisition of Plexikon for up to US\$935 million.

US M&As, 2006-10

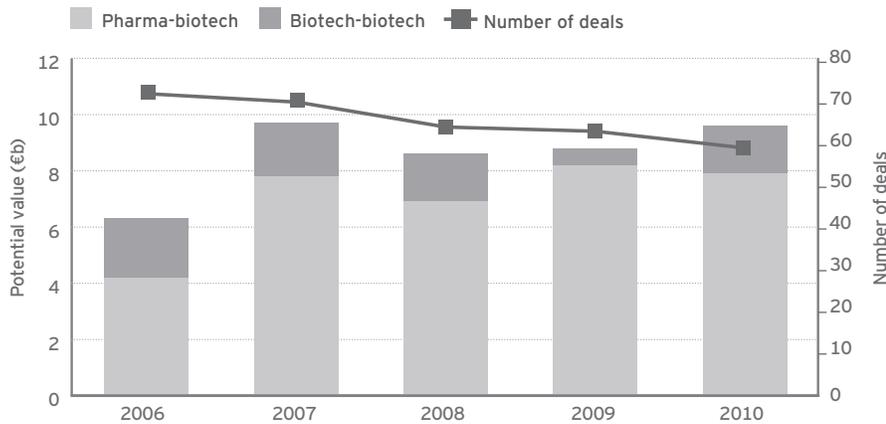


Source: Ernst & Young, Windhover Information, MedTRACK and company websites

Chart excludes transactions where deal terms were not publicly disclosed. The 2010 totals also exclude Sanofi/Genzyme, because the parties did not agree on terms until 2011, and Grifols/Talecris, because the transaction was subject to continuing antitrust review risk in 2010.

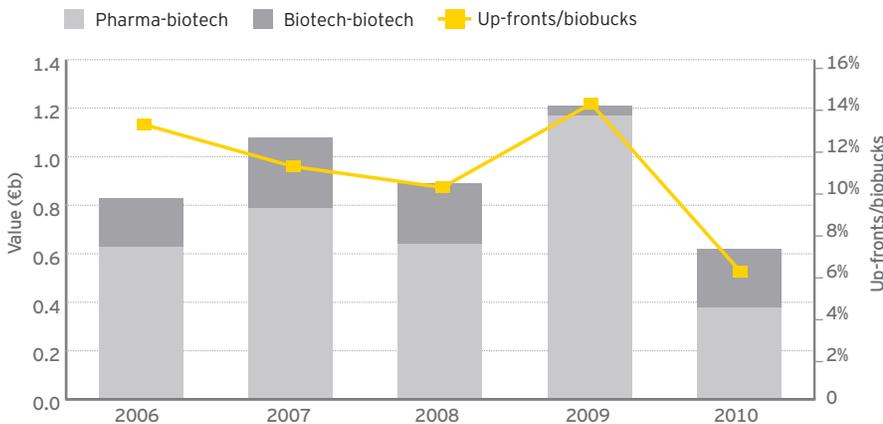
Europe

European alliances held steady on the biobucks front ...



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

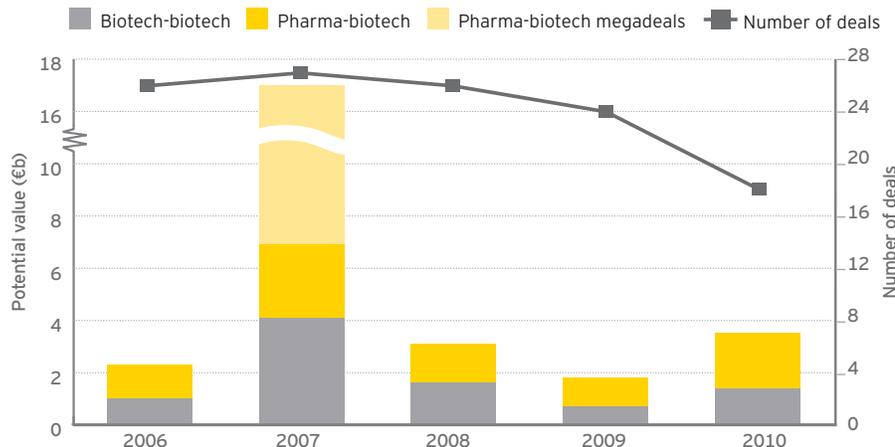
... but up-front payments declined to the lowest level in the last five years



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

While the total values of strategic alliances involving European biotech companies are lower than those involving US biotechs, the US trend of strong alliance activity (and total potential deal values) was also seen in Europe during 2010. However, while there was a steep decline in the number of transactions in the US, the number of strategic alliances held relatively steady in Europe. But as in the US, up-front payments fell quite dramatically in 2011 – both in absolute amounts and as a share of total potential deal values – as technology licensees became more cautious, especially for earlier-stage technologies, and sought to share the risk with biotech licensors.

European M&As, 2006-10



Source: Ernst & Young, Windhover Information, MedTRACK and company websites

The value of M&A transactions in Europe increased over the levels seen in 2008 and 2009. This was driven primarily by J&J's US\$2.3 billion acquisition of Crucell.

Canada

A number of significant licensing agreements were signed by Canadian biotech companies in 2010, with total potential biobucks in excess of US\$930 million. Three of these deals have potential values well over US\$100 million, while two others have values over US\$50 million:

- ▶ The largest Canadian biobucks deal (up to C\$330 million plus royalties) was an exclusive development and marketing agreement between Québec-based EndoCeutics and Bayer Healthcare.
- ▶ Transition Therapeutics and Eli Lilly and Company signed an agreement giving Transition exclusive worldwide rights to develop and potentially commercialize a class of compounds belonging to Lilly (with Lilly retaining the option to reacquire the rights until Phase II).
- ▶ Thallion Pharmaceuticals and LFB Biotechnologies signed a development and commercialization agreement giving Thallion up to C\$150 million plus royalties (with US\$2 million up front.)

- ▶ Québec-based ProMetic Life Science's agreement with Allist Pharmaceuticals gave Allist China rights to two drug candidates for US\$59 million in milestone payments plus royalties.
- ▶ Another Québec-based private company, AngioChem, signed a deal with Geron Corp., giving it US\$7.5 million up-front and US\$27.5 million in Geron stock.

On the M&A front, 2010 saw a mega-merger by Canadian standards – the US\$3.2 billion merger of Biovail Corp. and Valeant. Other than this transaction, M&A activity was fairly limited.



Australia

The deal scene was fairly heated down under, as 2010 saw some truly transformational strategic alliances in Australia's biotech industry. In March 2010, Acrux signed the largest deal in Australian biotech history. The Melbourne-based company's deal with Lilly is estimated to be worth US\$335 million and includes an up-front payment of US\$55 million. In November 2010, the FDA approval of Acrux's Axiron testosterone product triggered an US\$87 million milestone payment, with royalties to come.

But Acrux was not the only Australian company entering large deals in 2010. In December, Mesoblast closed an even larger deal with Cephalon. In exchange for granting Cephalon access to its unique stem cell technology, Mesoblast received US\$130 million up front, with potential milestone payments of up to US\$1.7 billion. (For insights on Cephalon's approach to deals, refer to our interview with Kevin Buchi on page 84.) Mesoblast closed the year with a market cap of A\$1.19 billion – the only Australian biotech, other than the industry-dominating CSL, to cross the billion-dollar market cap threshold. (For insights on the impact that such deals are having on the Australian financing landscape, refer to the article by Geoff Brooke on page 27.) ►



Dealing with options



Kevin Buchi
Cephalon
CEO

Even in an industry where alliances and acquisitions are commonplace, Cephalon has often stood out as a prolific deal maker. As the company's CEO – and its former CFO, COO and head of business development – Kevin Buchi has long been at the center of Cephalon's deal-making strategy. We caught up with Kevin in March 2011 to understand his company's approach to deals in light of current market challenges. Contemporaneous events confirmed that the pace of deals remains brisk. Leading up to our interview, Cephalon closed back-to-back transactions to acquire Gemin X and ChemGenex Pharmaceuticals. Soon after, things got even more heated when Valeant Pharmaceuticals made a bid to acquire Cephalon – a development that culminated in a more successful bid by Teva as we go to press.

Ernst & Young: What are the biggest challenges facing biotech companies today and how are they affecting your deal strategy?

Buchi: Drug development has become considerably more challenging. Development costs keep rising, while the regulatory approval process becomes increasingly stringent. It's not unusual for a promising drug to be delayed or in some cases rejected because more data is required. And, once a product is approved, it's increasingly difficult to get reimbursed by payers. Payers – who had once willingly paid for incremental improvements over currently available therapies – are starting to challenge that paradigm.

One answer is to focus on areas where there are both significant unmet medical needs and the costs to the health care system are high. Payers are more likely to pay for such treatments because they add considerable value to patients and reduce the overall cost to the health care system. Additionally, the commercialization costs are lower because you are dealing with a relatively limited number of specialist physicians. As a result, many of our transactions have been in areas such as lupus, eosinophilic asthma, congestive heart failure and sciatica – all areas that have little or no medical interventions and are associated with relatively high medical costs.

Another way in which we are mitigating risks and addressing challenges in the current climate is through option-based or staged deals. In recent years, we have used this approach in our transactions with Alba Therapeutics, BioAssets and Ception. In each case, the deal included a payment for the option to purchase the company at a later date. Such arrangements allow both parties to share the development risk, make it easier to bridge any valuation gaps, and give the inventor potential upside based upon success.

Ernst & Young: How do these option-based deals differ from in-licensing milestones or earn-outs/contingent value rights (CVRs) in the acquisition of a public company? Don't they all allow you to share risk based on success?

Buchi: Absolutely – there's nothing truly new in corporate finance! These structures are substantially similar; the differences may be in their relative emphasis. In a traditional licensing deal, the up-front tends to be fairly small and a lot of the value is on the back end. In option deals, the split may be closer to 50/50, while in CVRs there's usually a much bigger up-front investment with less on the back end. But each of them is a way to bridge the valuation gap and share risk.

Ernst & Young: What risks do you face in conducting deals and how do you mitigate them?

Buchi: The biggest risk is related to the tremendous uncertainties inherent in drug development – so you could pay a lot of money for an asset only to see it fail soon afterward. In addition, you never know as much about an asset you acquire as you do about something that you develop in-house – so due diligence is critical, and there is the risk of missing something that you should have caught. This is compounded by the "small company factor" – start-ups tend to be very capital-constrained and often cut corners to do R&D with limited capital resources.

Beyond trying to be comprehensive in our due diligence, we mitigate risk by taking a portfolio approach. Most of our deals have price tags that are less than 10% of our market capitalization. So even when something fails, it doesn't put the company at risk. Option deals further mitigate risk by limiting how much capital is placed at risk up front. But these structures can pose challenges of their own. Public investors or venture capitalists may prefer to cash out and move on instead of waiting for a contingency-based payment. So meeting everyone's needs can be challenging, and an outright purchase may work better in some settings. ▶

Adaptive strategies

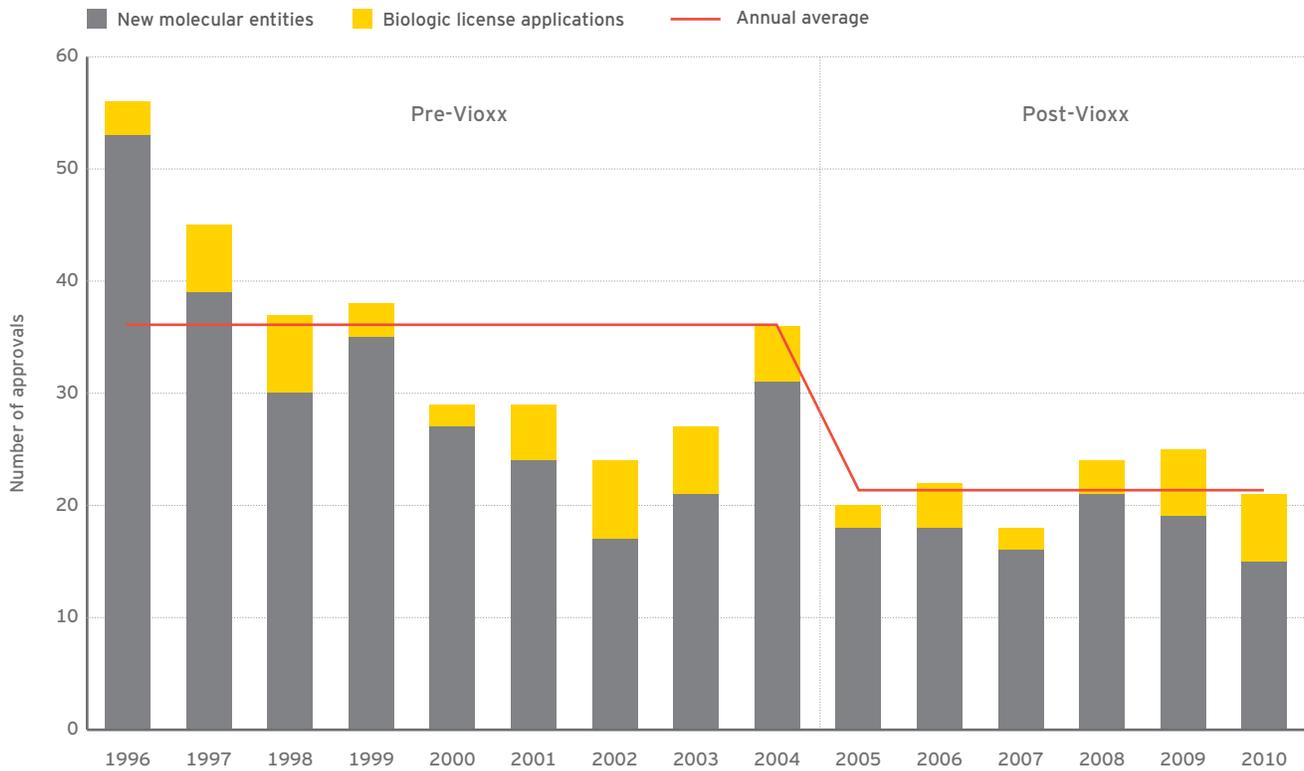
The big picture

The advancement of pipelines and the approval of new products are the tangible milestones of companies' R&D efforts and expenditures. New product approvals decreased industry-wide in 2010 as compared to 2009 and remained at a distressingly low level given the aggregate amount of R&D investment and the significant unmet needs of patients. In the absence of new and better drugs, demographic changes and the increasing incidence of chronic diseases will stretch government programs and budgets around the world. As noted in this year's *Introduction* article, biotech companies – as well as other stakeholders such as regulators – will need to be part of resolving this challenge.

While companies and regulators alike adapt strategies to address this productivity gap, clinical-stage pipelines remain robust, particularly in oncology, giving reason for some optimism. In fact, there is concern being expressed by some observers that the number of therapeutics addressing cancer indications will inevitably result in slower patient enrollment in new trials. Meanwhile, regulators are appropriately focused on value in making coverage decisions, which is causing companies at all stages of development to reassess their product development strategies to focus on true innovation and areas of unmet need.



FDA product approvals, 1996-2010



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

While it would not be fair to attribute the well-documented decline in R&D productivity and new drug approvals solely to the regulators, the regulatory pendulum clearly swung to emphasize risk in the risk-benefit equation following the withdrawal of Vioxx from the market in late 2004.

Selected outcomes-based pricing agreements, 2010

Drug	Indication	Company	Payer	Market	Description
CIMZIA	Rheumatoid arthritis	UCB	NHS	UK	UCB pays for the first 12 weeks of therapy, after which NHS pays for patients responding to the treatment.
RoACTEMRA (tocilizumab)	Rheumatoid arthritis	Roche	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.
IRESSA	Non-small cell lung cancer	AstraZeneca	NHS	UK	AZ will provide the product free for patients requiring less than three months of treatment. NHS will pay a fixed sum per patient for those requiring more than three months of treatment.
VOTRIENT	Kidney cancer	GlaxoSmithKline	NHS	UK	GSK reduces price of Votrient to bring it into line with Pfizer's Sutent and will give NHS a partial rebate if Votrient fails to match Sutent in clinical trials.
LUMIGAN (bimatoprost) and Combigan (brimonidine tartrate + timolol maleate)	Glaucoma	Allergan	Pharmac	New Zealand	In exchange for full funding and protection from delisting and subsidy reductions, Allergan will rebate some of its sales revenue back to Pharmac.
Vectibix (panitumumab)	Colorectal cancer treatment	Amgen	AIFA	Italy	In cases of therapeutic failure during the second month of treatment, Amgen will pay 50% of the cost, after which Amgen is not liable to pay treatment costs.
Proctosedyl (hydrocortisone with cinchocaine)	Hemorrhoids	Sanofi	Pharmac	New Zealand	Full funding in exchange for a confidential risk-sharing rebate.
KUVAN	hyperphenylalaninemia in patients with phenylketonuria	Merck KGaA	INAMI/RIZIV	Belgium	Merck KGaA will provide the first four weeks of treatment for free. After the first four weeks, Kuvan will be fully reimbursed for patients with a decrease of at least 30% in blood phenylalanine levels.
Nplate	Long-term immune thrombocytopenic purpura (ITP)	Amgen	INAMI/RIZIV	Belgium	Amgen will provide the first six weeks of treatment for free. Reimbursement will be stopped if Nplate has not shown efficacy within 16 weeks.

Source: Ernst & Young, Datamonitor, media reports

Governments around the globe – and particularly in Europe – are adopting policies which require companies to demonstrate improved health outcomes before approving high-priced drugs

for coverage. This trend has resulted in a number of risk-sharing agreements in recent years, and we can expect the incidence and variety of these arrangements to increase.

United States

Approvals by US companies, 2010

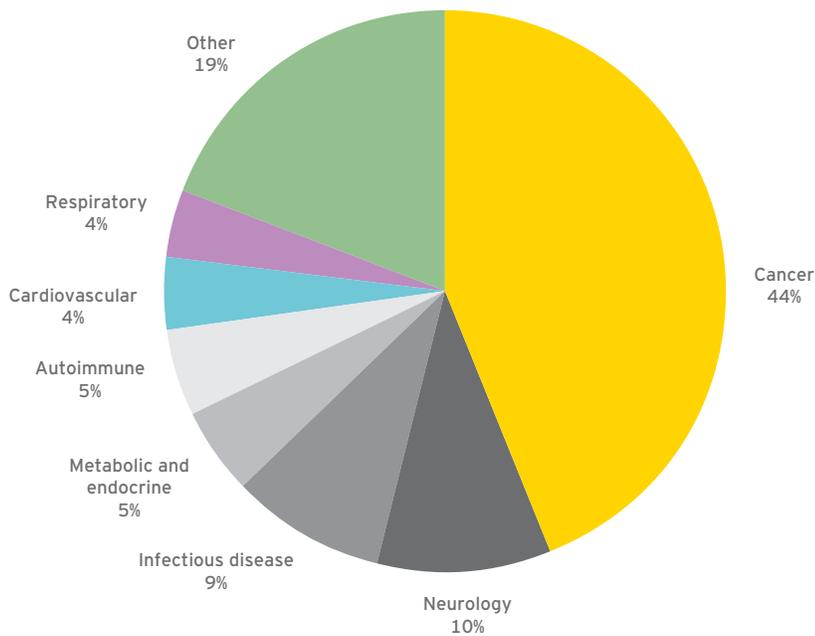
Company	Brand name	Generic name	Type of approval	Indication	Month	Orphan designation	Approved/registered in
Acorda Therapeutics	AMPYRA	Dalfampyridine	New molecular entity	Multiple sclerosis	January	Yes	US
Amgen	Prolia	Denosumab	Biologic license application	Postmenopausal osteoporosis	May/June		US and EU
Auxilium Pharmaceuticals (R&D collaboration with Pfizer; EU marketing)	XIAFLEX	Collagenase clostridium histolyticum	Biologic license application	Dupuytren's contracture	February	Yes	US
Bristol-Myers Squibb	SPRYCEL	Dasatinib	New molecular entity	Chronic myeloid leukemia	December	Yes	EU (previously approved in other markets)
Dendreon	PROVENGE	Sipuleucel-T	Biologic license application	Advanced prostate cancer	April	Yes	US
Forest Laboratories (Cereza)	Teflaro	Ceftaroline fosamil	New molecular entity	MRSA, bacterial pneumonia, skin infections	October		US
Genzyme	LUMIZYME	Alglucosidase alfa2	Biologic license application	Pompe disease	May	Yes	US
Pfizer	Prevnar 13	Pneumococcal 13-valent conjugate vaccine (Diphtheria CRM197 protein)	Biologic license application	Pneumococcal disease; otitis media	February		US (previously approved in other markets)
Savient Pharmaceuticals	KRYSTEXXA	Pegloticase	New molecular entity	Hyperuricemia	September	Yes	US
Vistakon Pharmaceuticals (Johnson & Johnson; Allergan has in-licensed)	LASTACFT	Vilast ophthalmic solution	New molecular entity	Allergic conjunctivitis	July		US
Merck Sharp Dohme/Cardiome Pharma	BRINAVESS	Vernakalant	Biologic license application	Recent onset of atrial fibrillation to sinus rhythm	September		EU

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

While in 2010 there were some highly anticipated approvals of new products originated by US companies, including Amgen's Prolia and Dendreon's Provenge, the overall low number reflected that companies of all sizes face an increasingly difficult environment for bringing products through development and to the market. Investors will focus attention on a number of important clinical milestones and pending approvals anticipated for 2011. One notable event not mentioned above was approval received by Momenta Pharmaceuticals and Sandoz of a generic version of the popular blood thinner Lovenox. Because the drug

(*enoxaparin*) is naturally derived and not as easily characterized as a typical chemical-based product, its approval was significant both as a validation of Momenta's technology platform and in its implications for future approvals of biosimilars attempting to demonstrate equivalence to branded products.

US clinical pipeline by indication, 2010



Source: Ernst & Young, MedTRACK and company websites

Cancer continues to dominate the US pipeline as companies increasingly pursue indications with high unmet need that do not require overly large clinical trial populations – thus requiring lower amounts of capital. Many companies are following a strategy of attempting to receive approval for a narrow, well-defined indication, with the intention of conducting post-approval trials in other indications with the same mechanism of action.



Europe

Selected approvals by European companies, 2010

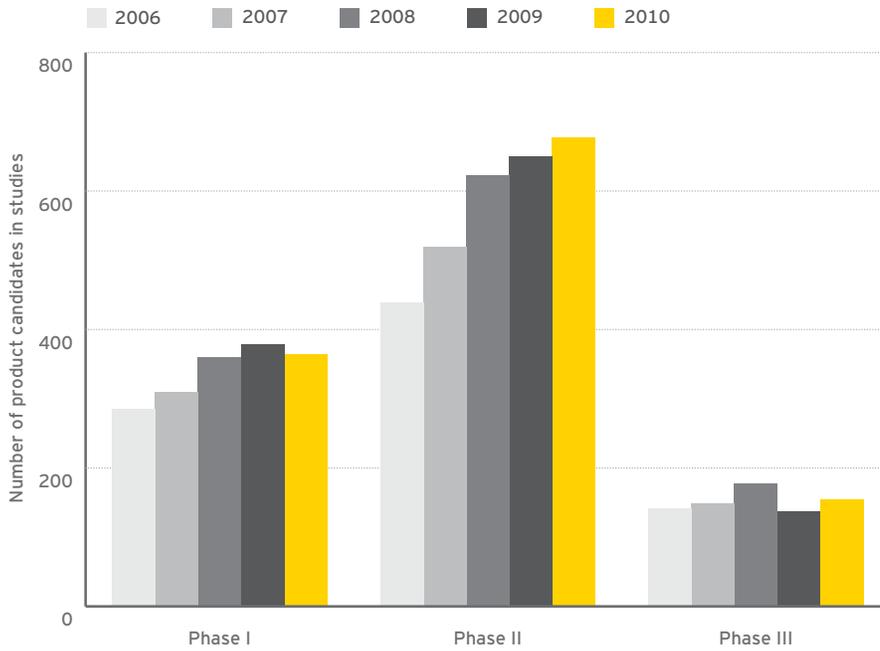
Company	Brand name	Generic name	Type of approval	Indication	Month	Orphan designation	Approved/registered in
Adienne	TEPADINA	Thiotepa	New molecular entity	Hematopoietic stem cell transplantation	March	Yes	EU
AOP Orphan Pharmaceuticals	TETMODIS	Tetrabenazine	New molecular entity	Huntington's disease	August		EU
Archimedes Pharma	PecFent	Fentanyl	New molecular entity	Pain associated with cancer	August		EU
AstraZeneca	BRILIQUE	Ticagrelor	Biologic license application	Acute coronary syndrome	December		EU
Bayer	Natazia	Estradiol valerate/dienogest tabs	New molecular entity	Pregnancy prevention	May		US
BioAlliance Pharma	Setofilm	Ondansetron	New molecular entity	Nausea and vomiting	March		16 European countries
BioPartners	Ravanex	Ribavirin	New molecular entity	Hepatitis C	April		EU
Boehringer Ingelheim	PRADAXA	Dabigatran	New molecular entity	Atrial fibrillation	October		US (previously approved in other markets)
Chemische Fabrik Kreussler	Asclera	Polidocanol	New molecular entity	Small varicose veins	March		US (previously approved in other markets)
HRA Pharma (licensed by Watson Pharmaceuticals)	ella	Ulipristal acetate	New molecular entity	Pregnancy prevention	August		US (previously approved in other markets)
Merz Pharmaceuticals	XEOMIN	IncobotulinumtoxinA	New molecular entity	Cervical dystonia	July		US (previously approved in other markets)
Novartis	Gilenya	Fingolimod	New molecular entity	Multiple sclerosis	September		US (previously approved in other markets)
Novo Nordisk	Victoza	Liraglutide	New molecular entity	Diabetes Type 2	January		US (previously approved in other markets)
Nycomed (licensed by Baxter in US)	TachoSil	Fibrin sealant patch	Biologic license application	Wound healing	April		US (previously approved in other markets)
Orphan Europe	Carbaglu	Carglumic acid	New molecular entity	Acute hyperammonemia	February	Yes	US (previously approved in other markets)
Pharming Group	Ruconest	Conestat alfa	Biologic license application	Hereditary angioedema	October	Yes	EU
Roche (R&D collaboration with Chugai)	ACTEMRA	Tocilizumab	Biologic license application	Rheumatoid arthritis	January		US (previously approved in other markets)
Sanofi	JEVTANA	Cabazitaxel	New molecular entity	Prostate cancer	June		US
Shire	VPRIV	Velaglucerase alfa IV	New molecular entity	Gaucher's disease	February	Yes	US

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

In aggregate, European companies had more new product approvals than their US counterparts. However, a significant number represented the US approval of drugs that had previously been approved in other markets. A noteworthy US approval was

Shire's VPRIV, which was approved to treat Gaucher's disease at a time when the only other therapy for this rare condition, Genzyme's Cerezyme, was facing supply constraints due to manufacturing problems.

Europe's Phase II pipeline has grown steadily over the last five years

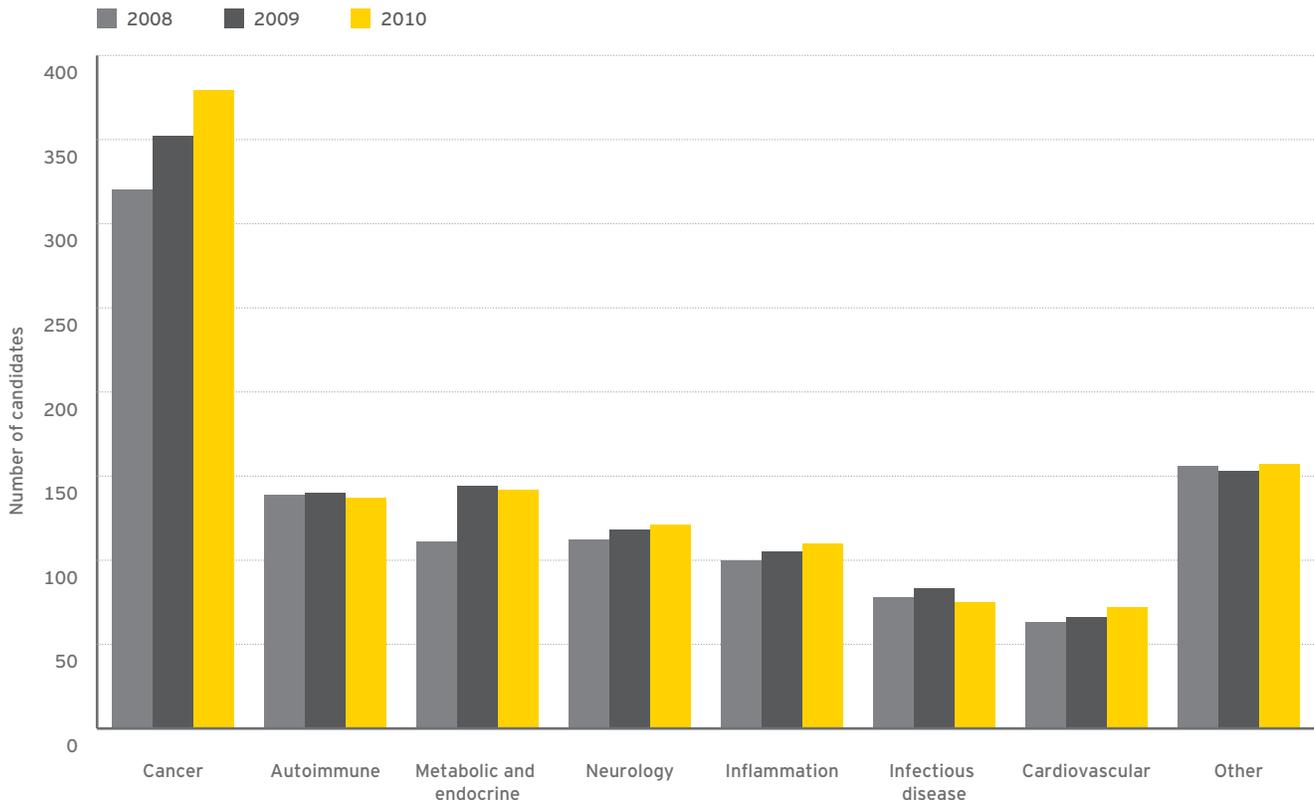


Source: Ernst & Young, MedTRACK and company websites

The Phase II pipeline of European biotechs has shown steady growth over the last five years. A significant portion of the industry's capital resources is focused on achieving proof-of-concept data necessary to license the products to larger players or to enable an M&A exit. The surging Phase II pipeline has not been matched by an increase in Phase III trials (or, for that matter, product approvals), due both to attrition as well as subsequent license/sale transactions.

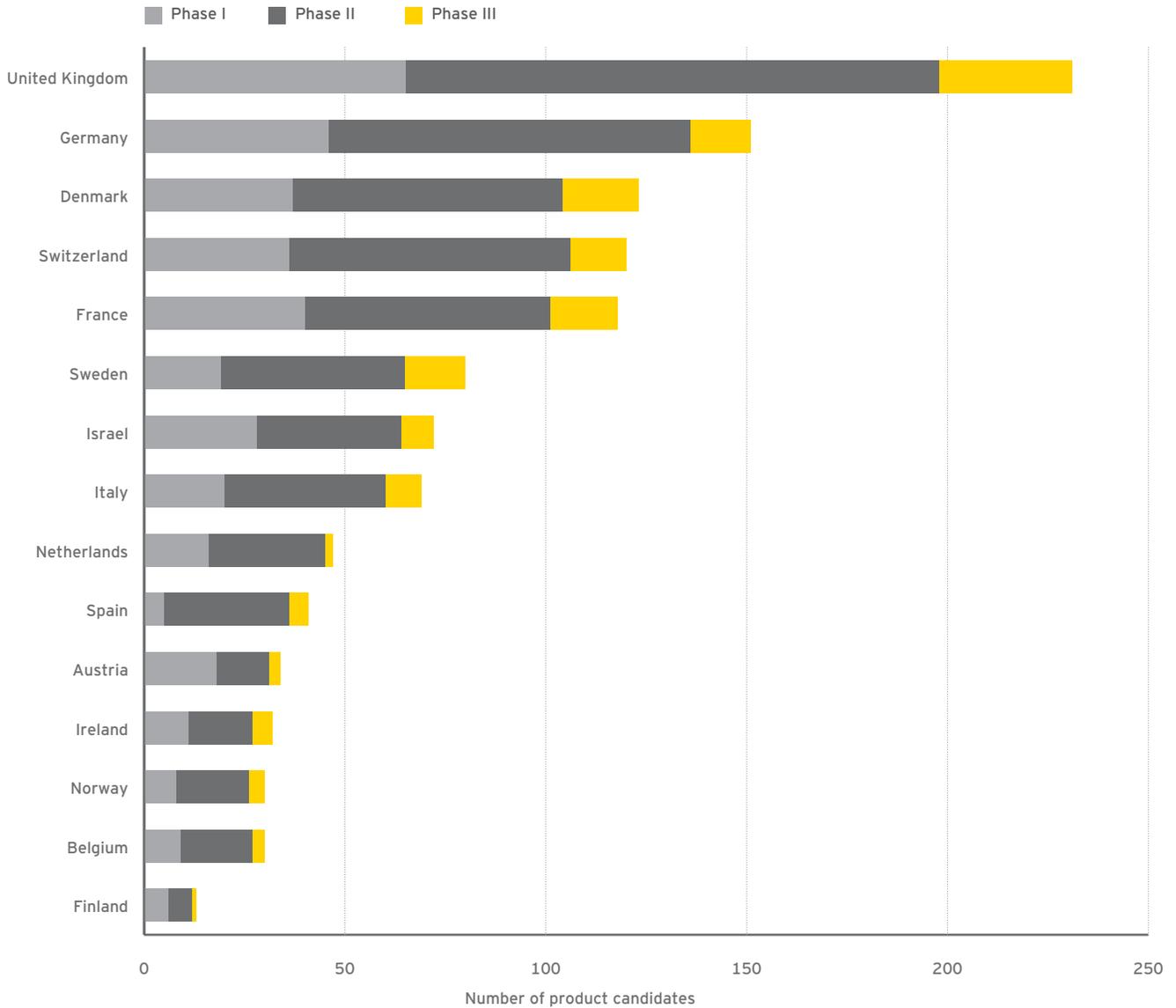
Consistent with the US, cancer is the dominant indication in European pipelines, growing steadily over the last three years.

Cancer is the largest and fastest-growing segment of Europe's pipeline



Source: Ernst & Young, MedTRACK and company websites

European clinical pipeline by country, 2010



Source: Ernst & Young, MedTRACK and company websites

While certain countries showed impressive gains in their pipelines (such as Austria's 31% increase and Spain's 17% increase), the majority of countries maintained their 2009 positions.

Acknowledgments

Project leadership

Glen Giovannetti, Ernst & Young's Global Biotechnology Leader, provided overall strategic vision for this project and brought his years of experience to the analysis of industry trends. Glen's perspective and insights helped define many of the themes we explore in the book. Beyond leadership, Glen brought a hands-on approach, writing articles and helping to compile and analyze data.

Gautam Jaggi, Managing Editor of the publication, directed the project, wrote or edited all of the articles and managed much of the data collection and analysis. Gautam developed several of the 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 content. 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.

Strategic direction

Special thanks to **Scott Morrison** and **Jürg Zürcher**, who continued to play a key role in the development of this publication, by providing invaluable strategic insights based on their long experience and a feel for the pulse of the industry.

Data analysis

The research, collection and analysis of European data and US financing, deal and pipeline data was conducted by **Ulrike Trauth**, **Nina Hahn**, **Eva-Marie Hilgarth** and **Christina Reufsteck**. **Gautam Jaggi** conducted analysis of financial performance data for US, Canada and Australia, with assistance from **Jimmy Zhong** of Ernst & Young's Center for Business Knowledge. **Winna Brown** and **Paul Karamanoukian** led the collection of Australian and Canadian financing data, respectively. Additional research was conducted by **Andrea Thomas**, **Erin Vasiloff** and **Martha Nagy**.

Jason Hillenbach, **Samir Goncalves**, **Ulrike Trauth**, **Amit Malik** and **Kim Medland** conducted fact checking and quality review of numbers throughout the publication.

Writing and editing assistance

The Australia and Canada sections were written by **Winna Brown** and **Paul Karamanoukian**, respectively. **Sue Carrington** provided writing assistance.

Amit Malik, **Saurabh Goel**, **Namrita Negi** and **Shraddha Arora** conducted research and drafted the country profiles. Additional research, writing and editing was conducted by **Sue Lavin Jones**, **Glen Giovannetti** and **Gautam Jaggi**. **Stanley Chang** (China), **Hitesh Sharma** (India) and **Yuji Anzai** (Japan) provided key insights, assisted by **Jian Luo** and **Simon Shi** (China) and **Himanshu Tanna**, **Rahul Patni** and **Shobhna Bakshi** (India). **Jon Hooper** led the writing of the New Zealand article.

Russ Colton was the lead copy editor for this project and was assisted by **Ellen Lask**. **Karla Brandt** proofread the document.

Design and layout

Christian Gonswa, the lead designer for this project, coordinated all aspects of design and art direction. Assisting Christian were **Oliver Voigt** (design and layout), **Christopher Tan** (custom illustration) and **Robert Fernandez** (chart illustration and layout). Additional design assistance was provided by **Giovanna Mantovani**, **Anthony Schadle** and **Rick Agostin**.

Marketing and support

Public relations efforts related to the book and its launch were led by **Sue Lavin Jones** and PR firm Feinstein Kean Healthcare's **Greg Kelley** and **Dan Quinn**.

Data for the charts on pages 4 and 5 were obtained from the following sources: Ernst & Young, company financial statements, BioCentury, VentureSource, US Food and Drug Administration, National Venture Capital Association, IMS Health, Centers for Medicare & Medicaid Services, Congressional Budget Office, World Health Organization, Espicom and Biotechnology Industry Organization.

Data exhibit index

Total US funding has rebounded after the downturn ...	2
... but a growing share has gone to mature, profitable companies	2
A growing gap: up-front payments have declined steadily in recent years	3
More web, less MD?	3
A capital agenda for the new normal	11
Select Chinese biopharmaceutical IPOs, 2010	28
Select Indian deals, 2010	30
Growth in established biotechnology centers, 2009-10 (US\$b)	37
Ernst & Young survival index, 2009-10	38
US biotechnology at a glance, 2009-10 (US\$b)	39
US biotechnology: commercial leaders and other companies (US\$b)	40
In 2010, the biotech industry slightly underperformed the market ...	41
... with smaller companies continuing to outperform large ones	41
After declining in 2008, smaller companies more than recovered ground	42
US companies with revenues greater than US\$500 million	43
The hunters and hunted? US drug development biotech companies by market cap	44
Selected 2010 US biotechnology public company financial highlights by geographic area (US\$m, % change over 2009)	45
European biotechnology at a glance, 2009-10 (€m)	48
European biotechnology: commercial leaders and other companies (€m)	48
The hunters and hunted? EU companies by market cap	49
European micro-cap stocks outperformed the other biotech companies	49
Selected 2010 European biotechnology public company financial highlights by country (€m, % change over 2009)	50
Canadian biotechnology at a glance, 2009-10 (US\$m)	51
Behind the numbers: the impact of the Biovail acquisition on Canadian biotech financial results	52
Australian biotechnology at a glance, 2009-10 (US\$m)	53
Capital raised in the US, Europe and Canada, 2000-10 (US\$m)	57
Distribution of capital raised in US, Europe and Canada by year	57
An exit too far? The median age of IPO companies has increased steadily	58
What are VCs funding? US and European seed and first-round financings over US\$5 million	59
US yearly biotechnology financings (US\$m)	60
Quarterly breakdown of 2010 biotechnology financings (US\$m)	60
Capital raised by leading US regions, 2010	61
The vast majority of US IPOs priced below their desired ranges	62

2010 US IPO performance	63
European yearly biotechnology financings (€m)	64
European corporate venture capital has increased since the financial crisis	65
... while Germany's family offices have become increasingly visible in the local market	65
European drug company IPOs have shifted toward later-stage companies	67
Quarterly breakdown of 2010 European biotechnology financings (€m)	67
Capital raised by leading European countries, 2010	68
Canadian yearly biotechnology financings (US\$m)	69
Capital raised by leading Canadian biotech clusters, 2010	69
Quarterly breakdown of 2010 Canadian biotechnology financings (US\$m)	70
Australian biotech public equity raised, 2002-10	71
US and European M&As, 2006-10	74
US and European strategic alliances remain strong based on biobucks	75
... while up-front payments declined sharply	75
Selected M&As, 2010	76
Deal premiums in acquisitions of public companies	76
Big biobucks alliances, 2010	78
Alliances with big up-front payments, 2010	78
Biotech acquisitions and alliances by big pharma companies (excluding mega-acquisitions), 2005-10	79
Strategic buyers: biotech acquisitions and alliances by big pharma companies, 2005-10	79
US strategic alliances remain strong based on biobucks	80
... while up-front payments declined sharply	80
US M&As, 2006-10	80
European alliances held steady on the biobucks front	81
... but up-front payments declined to the lowest level in the last five years	81
European M&As, 2006-10	81
FDA product approvals, 1996-2010	86
Selected outcomes-based pricing agreements, 2010	87
Approvals by US companies, 2010	88
US clinical pipeline by indication, 2010	89
Selected approvals by European companies, 2010	90
Europe's Phase II pipeline has grown steadily over the last five years	91
Cancer is the largest and fastest-growing segment of Europe's Phase III pipeline	91
European clinical pipeline by country, 2010	92

Global biotechnology contacts

Global Biotechnology Leader		Glen Giovannetti	glen.giovannetti@ey.com	+1 617 585 1998
Global Pharmaceutical Leader		Carolyn Buck Luce	carolyn.buck-luce@ey.com	+1 212 773 6450
EMEIA Life Sciences Leader		Patrick Flochel	patrick.flochel@ch.ey.com	+41 58 286 4148
Global Life Sciences Assurance Resident		Connie Austin	connie.austin@ey.com	+1 617 585 1912
Global Life Sciences Tax Leader		Neil Byrne	neil.byrne@ie.ey.com	+353 1 221 2370
Global Life Sciences Transaction Advisory Services Leader		Jeff Greene	jeffrey.greene@ey.com	+1 212 773 6500
Managing Editor of <i>Beyond borders</i>		Gautam Jaggi	gautam.jaggi@ey.com	+1 617 585 3509
Australia	Brisbane	Winna Brown	winna.brown@au.ey.com	+61 7 3011 3343
	Melbourne	Don Brumley	don.brumley@au.ey.com	+61 3 9288 8340
	Sydney	Gamini Martinus	gamini.martinus@au.ey.com	+61 2 9248 4702
Austria	Vienna	Erich Lehner	erich.lehner@at.ey.com	+43 1 21170 1152
		Isabella Schwartz-Gallee	isabella.schwartz-gallee@at.ey.com	+43 1 21170 1072
Belgium and the Netherlands	The Hague	Andrea Vogel	andrea.vogel@nl.ey.com	+31 88 40 74070
Brazil	São Paulo	Frank de Meijer	frank-de.meijer@br.ey.com	+55 11 2573 3383
Canada	Montréal	Paul Karamanoukian	paul.karamanoukian@ca.ey.com	+1 514 874 4307
		Lara Iob	lara.iob@ca.ey.com	+1 514 879 6514
	Edmonton	Trevor Lukey	trevor.d.lukey@ca.ey.com	+1 780 638 6644
	Toronto	Darrell Jensen	darrell.r.jensen@ca.ey.com	+1 416 943 2475
	Thornhill	Mario Piccinin	mario.piccinin@ca.ey.com	+1 905 882 3065
	Vancouver	Nicole Poirier	nicole.poirier@ca.ey.com	+1 604 891 8342
	Winnipeg	Tanis Petreny	tanis.l.petreny@ca.ey.com	+1 204 933 0251
China	Beijing	Stanley Chang	stan.chang@cn.ey.com	+86 10 5815 3628
Czech Republic	Prague	Petr Knap	petr.knap@cz.ey.com	+420 225 335 582
Denmark	Copenhagen	Benny Lynge Sørensen	benny-lynge.soerensen@dk.ey.com	+45 35 87 25 25
Finland	Helsinki	Timo Virkilä	timo.virkila@fi.ey.com	+358 207 280 190
France	Paris	Philippe Grand	philippe.grand@fr.ey.com	+33 4 78 17 57 32
		Pascale Auge	pascale.auge@fr.ey.com	+33 1 46 93 77 23
		Brigitte Geny	brigitte.geny@fr.ey.com	+33 1 46 93 6760
Germany	Mannheim	Siegfried Bialojan	siegfried.bialojan@de.ey.com	+49 621 4208 11405
	Munich	Elia Napolitano	elia.napolitano@de.ey.com	+49 89 14331 13106
India	Mumbai	Murali Nair	murali.nair@in.ey.com	+91 22 61920000
		Hitesh Sharma	hitesh.sharma@in.ey.com	+91 22 61920620
		Ajit Mahadevan	ajit.mahadevan@in.ey.com	+91 22 61920000
Ireland	Dublin	Nick Redmond	nick.redmond@ie.ey.com	+353 1 221 2322
		Neil Byrne	neil.byrne@ie.ey.com	+353 1 221 2370
Israel	Tel Aviv	Yoram Wilamowski	yoram.wilamowski@il.ey.com	+972 3 623 2519
Italy	Milan	Lapo Ercoli	lapo.ercoli@it.ey.com	+39 02 7221 2546

Japan	Tokyo	Hironao Yazaki	yazaki-hrn@shinnihon.or.jp	+81 3 3503 2165
		Yuji Anzai	anzai-yj@shinnihon.or.jp	+81 3 3503 1100
New Zealand	Auckland	Jon Hooper	jon.hooper@nz.ey.com	+64 9 300 8124
Norway	Trondheim/Oslo	Willy Eidissen	willy.eidissen@no.ey.com	+47 918 63 845
Poland	Warsaw	Mariusz Witalis	mariusz.witalis@pl.ey.com	+48 225 577950
Singapore	Singapore	Swee Ho Tan	swee.ho.tan@sg.ey.com	+65 6309 8238
South Africa	Johannesburg	Sarel Strydom	sarel.strydom@za.ey.com	+27 11 772 3420
Sweden	Uppsala	Björn Ohlsson	bjorn.ohlsson.uppsala@se.ey.com	+46 18 19 42 22
Switzerland	Basel	Jürg Zürcher	juerg.zuercher@ch.ey.com	+41 58 286 84 03
United Kingdom	Bristol	Matt Ward	mward@uk.ey.com	+44 11 7981 2100
	Cambridge	Cathy Taylor	ctaylor@uk.ey.com	+44 12 2355 7090
		Rachel Wilden	rwilden@uk.ey.com	+44 12 2355 7096
	Edinburgh	Mark Harvey	mharvey2@uk.ey.com	+44 13 1777 2294
		Jonathan Lloyd-Hirst	jllloydhirst@uk.ey.com	+44 13 1777 2475
	London/Reading	Ian Oliver	ioliver@uk.ey.com	+44 11 8928 1197
United States	Boston	Michael Donovan	michael.donovan1@ey.com	+1 617 585 1957
		Bruce Bouchard	bruce.bouchard@ey.com	+1 617 585 6890
	Chicago	Jo Ellen Helmer	joellen.helmer@ey.com	+1 312 879 5262
	Dallas	Kenneth Bernstein	kenneth.bernstein@ey.com	+1 214 969 8903
	Houston	Carole Faig	carole.faig@ey.com	+1 713 750 1535
	Los Angeles	Abdul Lakhani	abdul.lakhani@ey.com	+1 213 977 3070
		Don Ferrera	don.ferrera@ey.com	+1 213 977 7684
	New York/New Jersey	Tony Torrington	anthony.torryngton@ey.com	+1 732 516 4681
		Tony Masherelli	anthony.masherelli@ey.com	+1 732 516 4719
	Orange County	Dave Copley	david.copley@ey.com	+1 949 437 0250
		Kim Letch	kim.letch@ey.com	+1 949 437 0244
	Palo Alto	Scott Morrison	scott.morrison@ey.com	+1 650 496 4688
		Chris Nolet	chris.nolet@ey.com	+1 650 496 1620
	Philadelphia	Steve Simpson	stephen.simpson@ey.com	+1 215 448 5309
		Howard Brooks	howard.brooks@ey.com	+1 215 448 5115
	Raleigh	Michael Constantino	michael.constantino@ey.com	+1 919 981 2802
	San Antonio	David King	david.king02@ey.com	+1 210 242 7108
	San Diego	Dan Kleeburg	daniel.kleeburg@ey.com	+1 858 535 7209
		Jodi Hernandez	jodi.hernandez@ey.com	+1 858 535 7292
	Seattle	Kathleen Smith	kathy.smith@ey.com	+1 206 654 6305
	Washington, D.C.	Rene Salas	rene.salas@ey.com	+1 703 747 0732
		Chris Caffrey	chris.caffrey@ey.com	+1 703 747 1318

About Ernst & Young

Ernst & Young is a global leader in assurance, tax, transaction and advisory services. Worldwide, our 141,000 people are united by our shared values and an unwavering commitment to quality. We make a difference by helping our people, our clients and our wider communities achieve their potential.

Ernst & Young refers to the global organization of member firms of Ernst & Young Global Limited, each of which is a separate legal entity. Ernst & Young Global Limited, a UK company limited by guarantee, does not provide services to clients. For more information about our organization, please visit www.ey.com.

© 2011 EYGM Limited.
All Rights Reserved.

EYG no. FN0007

1103-1235313 LA



Ernst & Young is committed to reducing its impact on the environment. This document has been printed using recycled paper and vegetable-based ink.

This publication contains information in summary form and is therefore intended for general guidance only. It is not intended to be a substitute for detailed research or the exercise of professional judgment. Neither EYGM Limited nor any other member of the global Ernst & Young organization can accept any responsibility for loss occasioned to any person acting or refraining from action as a result of any material in this publication. On any specific matter, reference should be made to the appropriate advisor.

www.ey.com/beyondborders



Mixed Sources

Product group from well-managed forests and other controlled sources
www.fsc.org Cert no. SCS-COC-00867
© 1996 Forest Stewardship Council